Emotional Modulation of Cognition in Recent Onset Schizophrenia

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Chapter 1

General introduction

1

Schizophrenia is a severe mental disorder characterized by cognitive deficits, delusions, hallucinations, disorganized speech and behavior, lack of drive and diminished emotional expression (APA, 2000; Fioravanti, Bianchi, & Cinti, 2012; Tandon et al., 2013). Schizophrenia affects functioning in many different areas of life, such as health, daily living activities, work and social relationships (van Os & Kapur, 2009). Although schizophrenia cannot be cured, the prognosis has improved over the last decades in the sense that more patients are treated ambulatory and if admission is necessary, it is usually relatively brief (van Os & Kapur, 2009). Yet, life expectancy is still 10 to 25 years shorter than in healthy controls, due to, for example increased cardiovascular risk (Laursen, Munk-Olsen, & Vestergaard, 2012) and increased suicide risk (van Os & Kapur, 2009).

When Bleuler first described the syndrome of schizophrenia over a hundred years ago, he made a distinction between symptoms that are present during the whole course of the disease (fundamental symptoms) and symptoms that are only temporally present or not at all (accessory symptoms) (van den Bosch, 2011). While delusions, hallucinations and catatonia are referred to as accessory symptoms, the fundamental symptoms include a loosening of associations and impairments in cognition, affectivity, and subjective experiences (Peralta & Cuesta, 2011).

The course and outcome of individual patients is difficult to predict (van Os & Kapur, 2009). Outcome depends on many different factors and although some of the factors are known (symptom severity, use of medication, presence of a support system, severity of cognitive deficits), many remain unknown. The functional and occupational outcome of patients with schizophrenia depends more on disorganization (Sigaudo et al., 2014), verbal memory (Toulopoulouand & Murray, 2004), impairments in social cognition (Williams et al., 2008) and emotion processing (Kee, Green, Mintz, & Brekke, 2003) than on psychotic symptoms (Gonzalez-Blanch et al., 2008).

Cognitive deficits in schizophrenia

Patients with schizophrenia show significant cognitive impairments when compared to healthy subjects on several domains (Aleman, Hijman, de Haan, & Kahn, 1999; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). There are impairments in global cognitive functioning and in specific cognitive domains such memory functioning (including working memory, short-term memory and long term memory), language, executive function and attention (Fioravanti et al., 2012). The cognitive deficits are more severe when the disorder manifests itself in early rather than in late life and they appear to be relatively stable over the course of the disease (Fioravanti et al., 2012; Mesholam-Gately et al., 2009; Rajji & Mulsant, 2008). These cognitive deficits are related to functional outcome (Fujii & Wylie, 2003; Hofer et al., 2005; Williams et al., 2008) and quality of life (Fiszdon, Choi, Goulet, & Bell, 2008; Sota & Heinrichs, 2004) This makes cognitive deficits important targets for new pharmacological (Green & Nuechterlein, 2004) and non-pharmacological treatment

strategies (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). This thesis focusses on the cognitive domains of attention and short- and long-term memory. We chose to focus on these domains because attention (Prouteau et al., 2004; Williams et al., 2008) and memory (Fujii & Wylie, 2003; Hofer et al., 2005) are related to functional outcome and we wanted to investigate the interaction between cognition and different kinds of emotional stimuli. For language it is not possible to incorporate different kinds of emotional stimuli and the interaction between emotion and working memory or executive function is already studied elsewhere.

Many studies have demonstrated that performance on memory tasks is impaired in patients with schizophrenia compared to healthy controls (Aleman et al., 1999; Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Mesholam-Gately et al., 2009). This is regarded as a fundamental symptom in schizophrenia since deficits are present in the early course of the disease (e.g. Albus et al., 2006; Townsend & Norman, 2004) even before the start of medication (Hill, Beers, Kmiec, Keshavan, & Sweeney, 2004) and remain stable during the course of the disease (Tyson, Laws, Roberts, & Mortimer, 2005). In patients with schizophrenia the self-initiation of encoding strategies is defective, but not the execution of encoding strategies (Danion, Huron, Vidailhet, & Berna, 2007). Although overall memory performance is influenced by disturbances on other cognitive domains such as speed of processing and organization, this can only in part account for the differences between patients with schizophrenia and healthy controls in memory performance (Dickinson, Ragland, Gold, & Gur, 2008; Holthausen et al., 2003). This makes memory impairments a primary deficit in schizophrenia. There remains some debate in the literature about which memory domains are most affected: long or short term memory, verbal or visual memory and retrospective or prospective memory (Danion et al., 2007; Ordemann, Opper, & Davalos, 2014; Ranganath, Minzenberg, & Ragland, 2008) and the methodological strategies best used to test these differences (Leavitt & Goldberg, 2009).

Another fundamental cognitive deficit in schizophrenia is an impairment in attentional functions (Fioravanti et al. (2012); Heinrichs & Zakzanis, 1998). However, attention is so closely related to other cognitive domains such as working memory and executive function that impaired performance on almost any task could be interpreted as a proof for impairments in attention (Luck & Gold, 2008). Furthermore, attention has several sub-processes that are differentially impaired in schizophrenia (Braff, 1993) and could be differentially related to emotional deficits. Two of the subdomains of attention that are clearly impaired in SC and their relatives are sustained and selective attention (Filbey et al., 2008; Mulet et al., 2007).

Deficits in sustained attention (or vigilance) as measured with the Continuous Performance Task (CPT) are often replicated (Chen & Faraone, 2000), present in healthy family members of SC (Chen & Faraone, 2000) and relate closely to functional outcome in schizophrenia (Green, Kern, Braff, & Mintz, 2000) in both early psychosis patients

(Williams et al., 2008) and chronic schizophrenia patients (Prouteau et al., 2004). There is some discussion about the stability of deficits in sustained attention over the course of the disease (Irani et al., 2011; Mesholam-Gately et al., 2009) making them an important domain to study in ROS.

Selective attention, the ability to process a relevant stimulus while ignoring irrelevant environmental stimuli, is another subdomain that is disturbed in SC (Nuechterlein, Pashler, & Subotnik, 2006). Selective attention is often tested with the Color-Word-Stroop-Task (Stroop, 1935) (as mentioned above, attention is closely related to other cognitive domains and in the case of the Stoop task it is closely related to executive functioning, see (Henik & Salo, 2004)). In the Stroop task participants are required to read words while ignoring the color of the ink the words are written in. The classic Stroop affect is a facilitation effect when the meaning of the word and the color of the ink are congruent, so RED written in red, and an interference effect when the meaning of the word and the color of the ink are incongruent, so RED written in blue. In a review Henik and Salo (2004) reported augmented interference in the classic card version and augmented facilitation, but no augmented interference in the single trial computerized version.

Emotional disturbances in schizophrenia

Patients with schizophrenia suffer from several impairments that are related to emotions. Although there has been much debate about what "emotion" exactly is, an definition that is useful for cognitive research in schizophrenia, is given by Kring and Caponigro (2010): *"emotions are responses to events, whether internal or external, that consist of multiple components including outward expression (e.g., a smile), reported experience (e.g., reporting feelings of happiness), physiology (e.g., increased heart rate), appraisal (e.g., labeling one's experience and its probable cause), and brain activation (e.g., activation in certain areas of the prefrontal cortex)"*. Although diminished emotional expression is a diagnostic criterion (APA, 2000) and anhedonia seems to be clearly present in clinical practice, laboratory studies show that emotion deficits are subtle and are interwoven with cognitive deficits (Kring & Caponigro, 2010).

Processing of facial emotional expressions is less efficient in schizophrenia (e.g. Kohler, Walker, Martin, Healey, & Moberg, 2009; Morris, Weickert, & Loughland, 2009), especially when faces display negative emotions such as anger or fear (Scholten, Aleman, Montagne, & Kahn, 2005). Patients with schizophrenia are also impaired in using facial cues for social judgment (Marwick & Hall, 2008). These deficits are not attributable to a deficit in general cognition (Goghari, Macdonald, & Sponheim, 2010) and are already present in recent onset schizophrenia patients (Edwards, Pattison, Jackson, & Wales, 2001; Herbener, Hill, Marvin, & Sweeney, 2005). It has been suggested, that deficits get worse as the disease progresses (Mueser, Penn, Blanchard, & Bellack, 1997). Functional neuroimaging studies show that facial emotion processing is associated with a reduced BOLD-signal change in the amygdala (Gur et al., 2002)

and Aleman and Kahn (2005) proposed a model where a problem in the amygdala combined with less interconnectivity with the prefrontal cortex causes affective flattening and emotion recognition deficits.

Other parts of emotional experience appear to be intact in patients with schizophrenia. When they rate emotional stimuli for valence and arousal, most studies find that patients rate the stimuli the same as healthy controls (Burbridge & Barch, 2007). This holds true for visual emotional stimuli (Hempel et al., 2005; Pinheiro et al., 2013) including pictures from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2001), but also for emotional words. (Jalenques, Enjolras, & Izaute, 2013). Physiological responses (breathing rate, skin conductance response and systolic blood pressure) are also the same in SC as in healthy controls (HC) when exposed to emotional stimuli (Hempel, Tulen, van Beveren, Mulder, & Hengeveld, 2007).

Although the emotional experience when stimuli are presented seems to be intact, SC often suffer from a reduced ability to experience pleasure in general; anhedonia (Burbridge & Barch, 2007). One possible explanation is that they experience less pleasure when anticipating future events (Kring & Caponigro, 2010). This is in line with the theory by Herbener, Song, Khine, and Sweeney (2008) that emotion deficits in SC are not present at initial processing of stimuli but occur later and involve the effective integration of emotion and cognition.

The domain of social cognition is related to, but distinct from, both (neuro)cognition and emotion. Social cognition refers to the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others; weighing social situational factors in making inferences about other people's beliefs, emotions and intentions (Green & Leitman, 2008). Deficits in social cognition are already present in recent onset schizophrenia patients (Bliksted, Fagerlund, Weed, Frith, & Videbech, 2014) and appear to be a better predictor of social functioning than (neuro)cognition in schizophrenia (Fett et al., 2011).

Emotion cognition interaction in schizophrenia

Whether there are impairments in the interaction between emotion and cognition in patients with schizophrenia is less clear, although it has received more and more attention over the last decade. At the neural level cognitive and emotional processes share important physiological features, which could mean that disruptions in brain areas (such as the prefrontal cortex) can affect both cognition and emotion and also the interaction between these processes in SC (Anticevic, Repovs, & Barch, 2012). The interaction between emotion and working memory has been studied at the behavioral level and the level of brain activity by several authors. They found that despite deficits in emotion classification (Linden et al., 2010) or altered dorsolateral prefrontal cortex and hippocampal activity (Becerril & Barch, 2011), at the behavioral level working memory is influenced by emotion in the same way in SC as in HC. In HC memory

is usually better for *"emotionally charged stimuli"* than for *"emotionally neutral stimuli"* (Kensinger, 2004); emotional memory enhancement. Some studies have investigated this process in schizophrenia but their results are inconsistent and sometimes contradict, possibly due to methodological differences (Herbener, 2008). Although the literature on the interaction between emotion and attention in schizophrenia has grown in recent years (e.g. Anticevic et al., 2012; Dichter, Bellion, Casp, & Belger, 2010), there remains uncertainty about the reciprocal influence of emotion and attention in early psychosis patients. Strauss et all (Strauss, Allen, Duke, Ross, & Schwartz, 2008) suggest that *"impaired automatic processing may be core to diminished emotional experience"* in schizophrenia patients with prominent negative symptoms, since they found less interference from emotional words on an emotional Stroop task in patients with predominantly negative symptoms.

Outline of the thesis

The aim of this thesis is to increase our understanding of the interplay between emotion and cognition in recent onset schizophrenia patients (ROS). By examining only male ROS, effects of long-term use of antipsychotics, gender differences and effects of chronicity of the disorder as cofounders are reduced, giving more insight into the extent to which possible impairments are already present in the early phases of schizophrenia. This thesis describes a number of studies designed to evaluate the ways different emotion inducing stimuli and social cues modulate several (neuro)cognitive functions.

Chapter 2 describes a study designed to investigate the influence of emotion on sustained attention in healthy controls. Performances on a regular letter continuous performance task (AX-CPT) is compared to performance on an emotional continuous performance task (E-CPT). We hypothesized that if a general effect of emotion on sustained attention is present, the influences of positive and negative facial expressions on accuracy and reaction time would be the same. If the effects are emotion specific, accuracy and reaction time would be moderated in a specific way after positive and negative cues; in negative trials faster reaction times and decreased accuracy and in positive trials the opposite effect. **Chapter 3** describes a study that uses the same E-CPT as described in **chapter 2**, but now it is used to investigate whether the influence of emotion on sustained attention is different in recent onset schizophrenia patients compared to healthy controls. We hypothesized that if in recent onset schizophrenia patients facial emotion recognition was impaired, they would suffer from less interference from emotional faces than healthy controls. We also measured positive and negative symptoms and overall well-being to investigate whether these factors were correlated with a possible deficit in the way emotion modulates attention in ROS. Next, the influence of emotional content of words on selective attention was studies in a different group of ROS and HC. They performed a Stroop task with both color and emotional words, of which the results are described in **chapter 4**. We

hypothesized that, unlike the study described in **chapter 3**, ROS would show a similar interference/facilitation effect for emotional words as HC, despite a general attentional deficit.

Because studies on emotional memory modulation in patients with schizophrenia report contradictory results we reviewed this literature to explore to which extent the contradictory results are caused by methodological differences. The results of this review are described in **chapter 5**. We also consider what we can learn about emotional memory modulation in patients with schizophrenia when we take these differences into account. The study into emotional memory modulation that followed the review is described in **chapter 6**. We tested long and short-term visual and verbal memory in a group of male ROS and compared their performance to age and gender matched HC. We hypothesized that emotional memory modulation would take different forms for visual and verbal stimuli in HC and ROS. Furthermore, if there are deficits in emotional memory modulation in ROS, we expected that these would be more prominent for long-term compared to short-term memory because of the deficits in consolidation.

In **chapter 7**, we describe a study that investigated the influence of social cues instead of emotional stimuli on cognition. We hypothesized that ROS would have a general cognitive deficit and would show the same Simon effect as HC, but that ROS would show less interference/facilitation from gaze direction (social cue) than HC. Again, we measured positive and negative symptoms to investigate whether these factors were correlated with a possible deficit in social cognition in ROS. Finally, the findings of the previous chapters are discussed and integrated in a summary, discussion and conclusion (**chapter 8**), followed by a Dutch (**chapter 9**) summery.

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Chapter 2

Different influences of positive and negative faces on attention

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in preparation for submission

Abstract

Both negative and positive salience of stimuli can influence attention, but the effect of facial expressions on the perception and processing of subsequent stimuli is less well understood. We investigated how sustained attention is influenced by positive and negative emotional expressions as task irrelevant stimulus properties.

69 healthy students performed an adapted version of the AX-Continuous Performance Task with faces instead of letters. Probe faces all displayed a neutral expression, while cue faces displayed angry, happy or neutral expressions.

Accuracy decreased in negative but not positive trials and reaction time was faster in both negative and positive trials. Both effects were only present with short (500ms) and not long (5000ms) interstimulus intervals and were enhanced by fatigue.

Our results show that all emotional expressions improve reaction time. The effect of facial expressions on accuracy is emotion specific; accuracy decreases after negative, but not after positive cue faces.

Introduction

Sustained attention, the ability to focus mental activity over prolonged periods of time, is important for all kinds of everyday tasks. Over the last decades the interaction between emotion and spatial attention has been studied extensively (Vuilleumier, 2005). Although earlier studies primarily investigated negative emotions, more recent studies also included positive stimuli but with more variable results (Vuilleumier & Huang, 2009). Behavioral findings indicate that both perception of, and attention to emotional stimuli is enhanced compared to neutral stimuli (Vuilleumier & Brosch, 2009). Although these effects can improve task performance (Anderson, 2005; Ohman, Lundqvist, & Esteves, 2001; Phelps, Ling, & Carrasco, 2006), they can also interfere with task performance (Vuilleumier & Brosch, 2009). There is interference because it is more difficult to disengage attention from emotional salient stimuli (Koster, Crombez, Verschuere, & De Houwer, 2004) and because emotional stimuli place a heavier demand on attentional resources (Yiend, 2010).

Overall, negative emotions narrow the field of view: attention and cognitive processing are focused centrally while peripheral encoding is decreased (Vuilleumier & Huang, 2009). Positive emotions appear to broaden the breadth of attention, promoting exploration of new information (Vuilleumier & Huang, 2009) at the cost of impaired central processing (Rowe, Hirsh, & Anderson, 2007); this is in line with the broadening hypothesis (Fredrickson, 1998).

Facial expressions are among the most ecological valid types of emotional stimuli, they can decrease detection thresholds for consecutive stimuli (Ciesielski, Armstrong, Zald, & Olatunji, 2010) and enhance contrast sensitivity for subsequent stimuli (Phelps et al., 2006).

Few studies however have focused on the interaction between emotional expressions and sustained attention in healthy controls. Those studies that did, usually included only negative or positive facial expressions, used schematic instead of "real" facial expressions or required participants to respond when an emotional stimulus was present, which can potentially cause a response bias. The objective of the present study was to investigate the influence of angry and happy facial expressions on sustained attention in healthy controls and compare them to neutral faces.

We predicted that if a general effect of emotion on sustained attention is present, the influences of positive and negative facial expressions on accuracy and reaction time would be the same; faster reaction times and decreased accuracy after all emotional cues. If the effects are emotion specific, accuracy and reaction time would react in a specific way after positive and negative cues; in negative trials faster reaction times and decreased accuracy and in positive trials the opposite effect.

Methods

Participants

Participants were 85 medical students from the Erasmus Medical

Centre in Rotterdam, the Netherlands. Inclusion criteria were: age between 18 and 30, and normal or corrected vision. Exclusion criteria were: current or previous psychiatric or neurologic disorder; first or second-degree relative with a psychiatric or neurologic disorder; illicit drug use. We used the Edinburgh Handedness Inventory (Oldfield, 1971) to determine handedness. Participants gave informed consent and the study protocol was approved by the local Medical Ethical Committee.

15 participants (7 males) were excluded based on the exclusion criteria, and 1 male participant for not complying with task instructions, leaving 69 participants (33 males) for analysis. Mean age was 23.5 years (range 18.8 – 29.8 years) and 8 participants were left-handed.

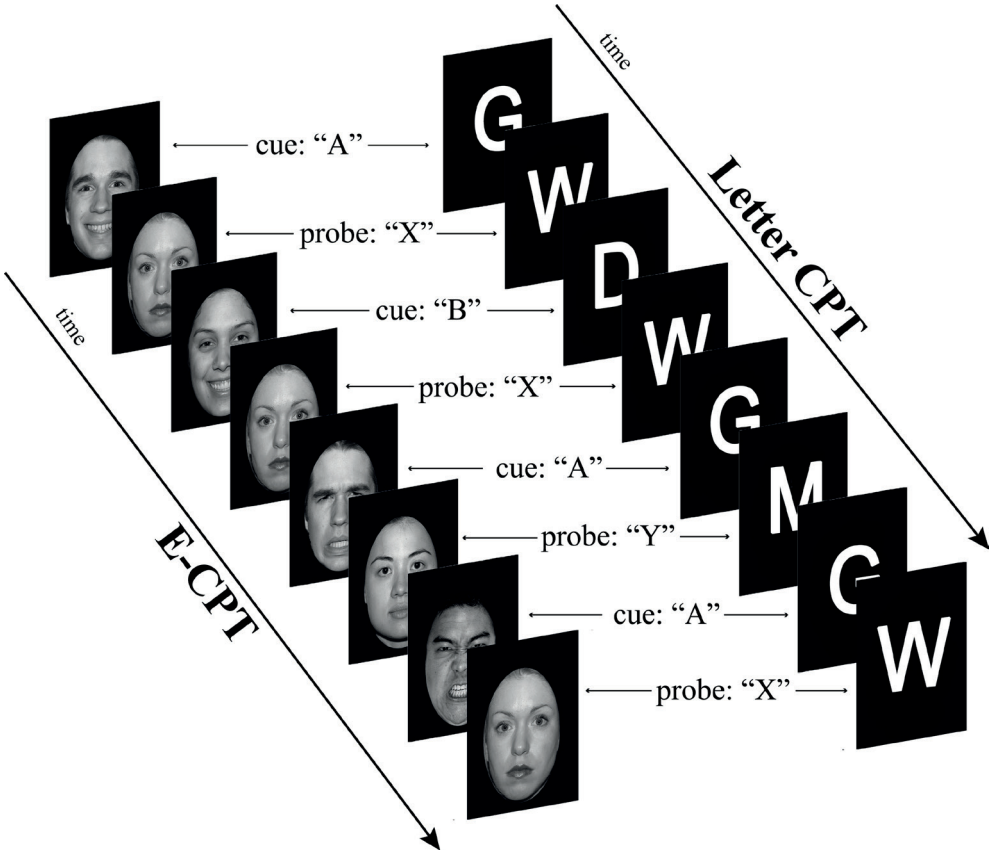
Letter CPT

For over 50 years, the Continuous Performance Test (CPT) has been used to study sustained attention (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). Our CPT was adapted from the AX-CPT used by Cohen et al. (1999) where participants view a series of letters and react to a specific probe letter, but only when it is preceded by a specific cue letter. We used two sets of consonant letters (C, Q, G, D) and (N, H, M, W) (figure 1), which are easy to discriminate between sets but difficult to discriminate within a set (Smid et al. 1991). G was our correct cue and C, Q and D were distracter cues (see figure 1). W was the correct probe and N, H and M were distracters. Participants were instructed to react to a W, but only when a G preceded it, and to refrain from responding when a W was preceded by a distracter cue or when a distracter probe followed a G. Thus, participants had to hold a cue in working memory until they analyzed the probe. Stimuli were presented sequentially as white single capital letters on a black background. All stimuli were presented for 500ms and the response window was 1000ms, starting at the onset of stimulus presentation. To control for a possible influence of working memory load on performance we varied the time participants had to hold the cue "online" in working memory; the interstimulus interval (ISI). In the short conditions the ISI was 500ms and there were 300 cue-probe pairs, making the task approximately 12 minutes. In the long conditions the ISI was 5000ms and there were 100 cue-probe pairs, making the task 18 minutes. Subjects were asked to answer as precisely and as fast as possible. Similar to Cohen et al. (1999), the ratio of target to non-target events was: 70%–30%.

Emotional CPT

For the emotional version of the CPT (E-CPT), we replaced the letters with portrait photos from the NimStim Face Stimulus Set (www.macbrain.org, 2011) (figure 1). We used black-and-white photos of European-American actors without facial hair. Hairstyle and clothing were removed, so sex discrimination was based only on facial features. Participants were instructed to respond to a specific face, but only when a face of the opposite sex preceded it.

Figure 1: Letter-CPT and E-CPT



Schematic representation of the Letter CPT and the Emotional CPT. Note that the photos used in figure 1 are not the actual stimuli used in the experiment in accordance with publication restrictions of the Research Network on Early Experience and Brain Development. We used modified photographs of models 1, 2, 3, 6, 8, 9, 20, 24, 27, 30, 33 and 37 from the NimStim database.

To investigate how emotion biases probe perception in a sustained attention task independent of explicit emotion appraisal, the cue faces displayed neutral, negative (angry) or positive (happy) expressions. The emotional expressions of the cues were task irrelevant stimulus properties and all probe-faces displayed neutral expressions; no emotional material was present at the time of responding, making the task process purely cognitive (Yiend, 2010).

To control for possible sex effects we used two versions of the task. Half of the participants performed version 1, where the correct probe was a specific female face and the correct cues were male. The other half performed version 2, where the correct probe was a specific male face and the correct cues were female faces. Again, all stimuli were presented for 500ms, the response window was 1000ms and the target to non-target ratio was: 70%–30%.

Procedure

Subjects were seated in a well-lit properly isolated room at approximately 60 cm distance from the 48 cm computer screen where stimuli were presented. Tasks were programmed with "Presentation" 13.1 software (Neurobehavioral Systems). Letters and photos were all resized to a size of 9.5° horizontally and 14° vertically. Participants responded by clicking the left mouse button with their right index finger. Because all left-handed participants used their right hand to control the mouse in everyday life, they also used their right hand in this experiment.
All participants performed a long and a short ISI version of both the Letter- and Emotional-CPT. Tasks were presented in pseudo-random order to correct for fatigue effects. Before each task participants performed a short practice trial to get accustomed to the response buttons and trial design.

Data Analysis

Signal detection models were used to analyze the data. For accuracy we calculated the A-prime-score (A') which is a more specific measure of overall accuracy than hit rate (Snodgrass & Corwin, 1988), because it also takes into account the percentage of false alarms.

Reaction Times (RT) were analyzed only for correct trials. Trials with a RT more than 3 standard-deviations from individual means were excluded from analysis. First, to compare the effect of replacing letters with faces, we performed an omnibus 2 by 2 repeated-measurement ANOVA for A' values and RT with task (Letter-CPT, E-CPT) and ISI (short, long) as within-subject variables. Secondly, to investigate the influence of emotion on performance on the E-CPT, we performed a 3 by 2 repeated measurement ANOVA for A' values and RT with emotion (neutral, negative and positive) and ISI (short, long) as within-subject variables. Significant effects were further evaluated with post hoc T-tests.

Results

Comparison of E-CPT with Letter CPT performance

Overall accuracy was lower on the E-CPT (0.963, SD 0.018) than the Letter CPT (0.980, SD 0.013) ($F(1,68) = 76.422$, $p < 0.001$, $\eta 2 = 0.529$). Unexpectedly, accuracy was lower in the short compared to the long ISI condition ($F(1,68) = 56.636$, $p < 0.001$, $\eta 2 = 0.454$), in both the Letter CPT (0.975 vs 0.985, $p < 0.001$) and the E-CPT (0.953 vs 0.973, $p < 0.001$). We found a significant interaction for task by ISI ($F(1,68) = 10.649$, $p = 0.002$, $\eta 2 = 0.135$); the accuracy difference between ISI conditions was larger in the E-CPT than the Letter CPT.

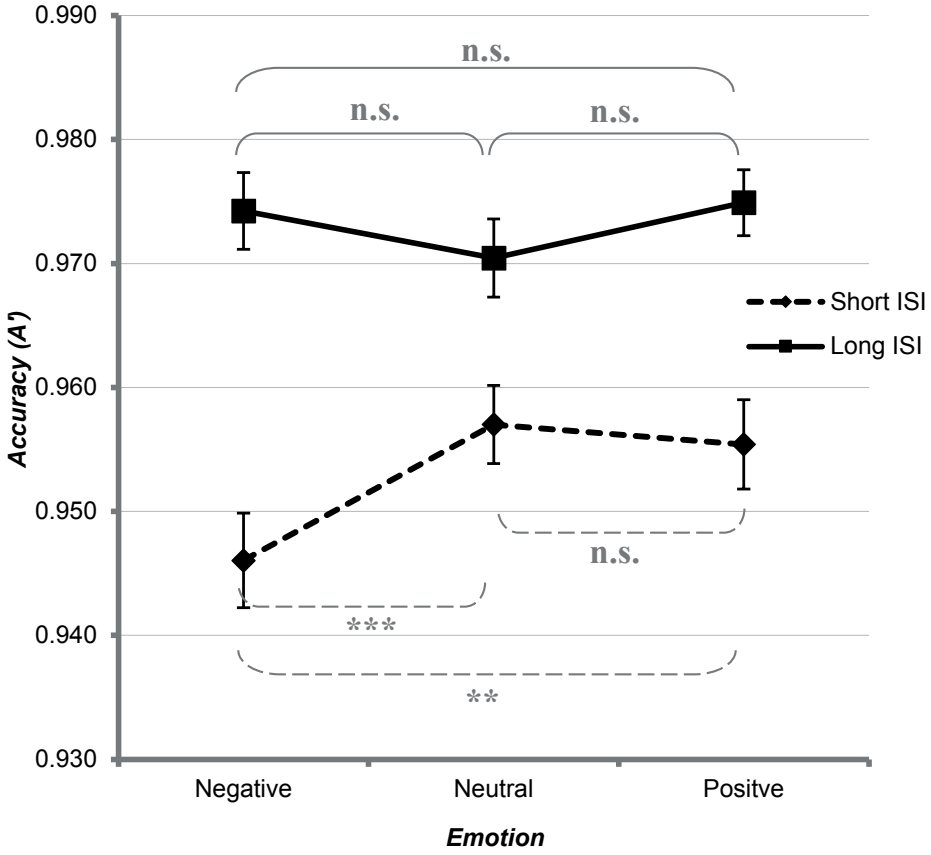
Overall RT was slower on the E-CPT (402ms, SD 59ms) than the Letter CPT (329ms, SD 48ms) ($F(1,68) = 335{,}741$ $p < 0.001$, $\eta 2 = 0.832$). Reaction time was faster in the short compared to the long ISI condition ($F(1,68) = 132.436$ $p < 0.001$, $\eta 2 = 0.661$) in both the Letter CPT (287ms vs 371ms, $p < 0.001$) and the E-CPT (363ms vs 441ms, $p < 0.001$).

There was no task by ISI interaction. We concluded that replacing the letters with faces did not change the test properties in our E-CPT.

Influence of emotion on accuracy

We found a main effect for ISI ($F(1,68) = 41.699$, $p < 0.001$, $\eta 2 = 0.380$). Post hoc T-tests revealed that accuracy was lower in the short than the long ISI condition (0.953 vs 0.973, $p < 0.001$). There was no main effect for emotion ($F(2,67) = 2.230$ $p = 0.111$, $\eta 2 = 0.032$). We found a significant interaction for emotion by ISI ($F(2,67) = 6.009$ $p = 0.003$, $\eta 2 = 0.081$). This interaction is based on a significantly lower accuracy in the short ISI condition for negative cues compared to positive ($t= 3.171$) and neutral cues ($t= 3.638$), while there were no accuracy differences within the long ISI condition, see also figure 2.

Figure 2: Accuracy for the different emotional stimuli of the E-CPT with standard errors of the mean and post-hoc t-tests.

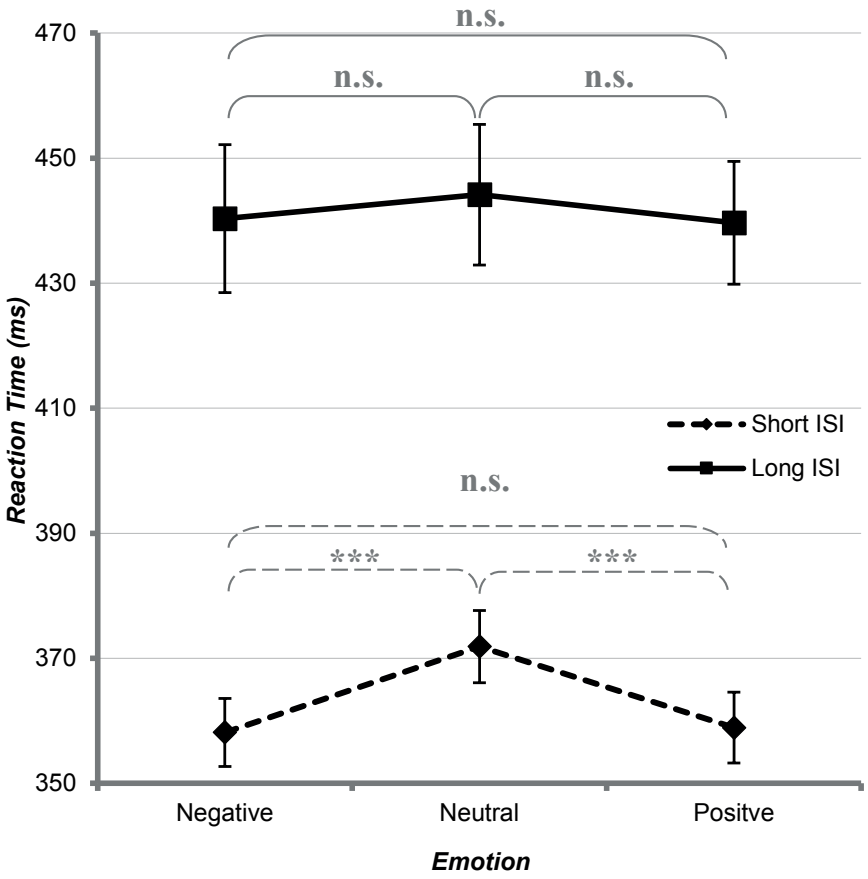


**: p < 0.05, **: p < 0.01, ***: p < 0.001, n.s.: not significant*

Influence of emotion on reaction time

We found a main effect for emotion ($F(2,67) = 10.614$ $p < 0.001$, $\eta 2 = 0.135$). RT was faster for both negative ($t = 4.454$) and positive ($t = 4.815$) compared to neutral cues. Decreases in RT were only significant in the short ISI condition ($F(1, 68)$ 67.097, $p < 0.001$, $\eta 2 = 0.497$). We found a trend level interaction for emotion by ISI ($F(2,67) = 2.875$ $p = 0.072$, $\eta 2 = 0.041$, see also figure 3). Post hoc t-test revealed once again, that the emotion effect was present in the short (positive vs. neutral: $t = 7.924$; negative vs. neutral: $t = 9.717$) but not long ISI condition.

Figure 3: Reaction time for the different emotional stimuli of the E-CPT with standard errors of the mean and post-hoc t-tests



**: p < 0.05, **: p < 0.01, ***: p < 0.001, n.s.: not significant*

Time course analysis

To investigate if the results in this sustained attention task were due to fatigue, we investigated the time course of the effects of emotion on accuracy and reaction time in a secondary analysis in the short ISI emotional CPT. We divided A' values and reaction times into three blocks where the first block contained data from the first 100 trials, the second block data from the middle 100 trials and the third block data from the last 100 trials. We performed a 3 (emotion; positive, negative and neutral) by 3 (first, second and third block) ANOVA for A' and RT. For accuracy we found a trend level effect for emotion ($F(2,67) = 2.383$ $p = 0.097$, $\eta 2 = 0.034$), a main effect for block ($F(2,67) = 12.751$ $p < 0.001$, $\eta 2 = 0.158$) and an interaction between block and emotion ($F(2,67) = 20.028$ $p < 0.001$, $\eta 2 = 0.228$).

Post hoc t-test revealed that accuracy for neutral trials decreased from the first (A' 0.973) to the second block (A' 0.945), but did not change further for block 3 (A' 0.956). For negative trials however, accuracy only decreased from the second (A' 0.968) to the third block (A' 0.924), while accuracy for positive trials did not change over time (A' 0.956, 0.954 and 0.955 respectively). This indicates that the effects of emotion on accuracy as described above were particularly evident in the third block.

For reaction time we found a main effect for emotion ($F(2,67) = 56.070$ $p < 0.001$, $\eta 2 = 0.452$), a trend level effect for block ($F(2,67) = 3.129$ $p = 0.0543$, $\eta 2 = 0.044$) and an interaction between block and emotion ($F(2,67) = 8.711$ $p < 0.001$, $\eta 2 = 0.114$). Post hoc t-test revealed that RT decreased slightly over time for positive (363ms, 360ms and 351ms) and negative trials (364ms, 357ms and 354ms), while RT for neutral trials was slower than emotional trials in block one (376ms), decreased for block 2 (365ms) but increased tot the level of block one for block three (376ms). This means that the effect of emotion on reaction time for sustained attention described above, again were particularly evident in the third block.

Discussion

We used a CPT with positive, negative and neutral facial expressions as cues to study the influence of negative and positive emotion on sustained attention. We found reduced accuracy and faster reaction times after negative cues. After positive cues reaction time was also faster, but without a reduction in accuracy. So it appears that the effect on accuracy is emotion specific; accuracy decreases after negative, but not after positive cue faces. There is a general effect of emotion on RT; RTs are faster after both positive and negative cue faces. These effects are more pronounced during the last part of the task, showing that when the demands on attention increase, the influence of emotion increases.

After seeing emotional expressions RT was faster. This could be a result of affective priming (Palermo & Rhodes, 2007) which means that seeing an emotional face causes the subsequent neutral probe face to be perceived as the same emotion. This effect is generally considered to

be brief (200-500 ms (Chun & Potter, 1995)), but neural responses to emotional stimuli can be prolonged beyond 500 ms in conditions of low attentional load (Vuilleumier & Huang, 2009). There is also some evidence that affective priming can influence memory up to 24h (Sweeny, Grabowecky, Suzuki, & Paller, 2009).

In a rapid serial visual presentation task, neutral words are also detected better when they follow a negative or a positive word (Steinmetz, Muscatell, & Kensinger, 2010). Both negative and positive words can alleviate the attentional blink, but only when they have a sufficiently high arousal value (Anderson, 2005). When using schematic faces in an attentional blink paradigm, the attentional blink is stronger but shorter for angry compared to happy faces (Maratos, 2011). The severity of the attentional blink is related to the effort it takes to consolidate the previous stimulus, because the visual system can only process one item at a time (Kihara, Yagi, Takeda, & Kawahara, 2011).

Fox and colleagues (Fox, Russo, & Dutton, 2002) studied spatial attention with a cueing task where angry, happy or neutral schematic faces were show as cues on the same or the opposite side of the screen from to the subsequent target. They found that participants had difficulty in disengaging from emotional stimuli, resulting in longer reaction times for emotional compared to neutral stimuli when the cues were on the opposite side. When the cues were presented on the same side, RTs did not differ between emotional and neutral faces.

Only negative expressions interfered with accuracy. Since negative stimuli capture more attention than positive stimuli (Eastwood, Smilek, & Merikle, 2003), negative cue faces might interfere with the processing of subsequent probes by placing a heavier demand on attentional resources (Yiend, 2010), resulting in lower accuracy. Ciesiellski et al. (2010) studied the temporal course of attention-emotion interactions and found that emotions impede accuracy more, when the time between the emotion and the stimulus is shorter, which is in line with our finding that the effect of emotion was only present at the short ISI.

Based on Cohen's AX-CPT (1999), we expected that accuracy would decrease with increasing working memory load, but in both our CPTs, accuracy was lower in the short than in the long ISI conditions. This difference could be a result of using stimuli that were harder to discriminate within sets. The decrease in accuracy in the short ISI condition could be a result of the fast pace combined with harder to discriminate probes. It demands more attention to update working memory at a high pace, but when it is updated, it does not matter how long simple cues are stored in working memory. This is supported by the fact that in the E-CPT, where the stimuli are even harder to discriminate within sets, accuracy differences between the two ISI conditions were larger. Another explanation why this effect was more prominent in our task is that in Cohen's study a ceiling effect seems to be present.

Combining the data, these results show that negative faces speed up processing but decrease processing efficiency for the subsequent

stimuli; a speed-accuracy trade off. However, positive stimuli also speed up processing, but without interfering with efficiency. Angry facial expressions induce a mode of processing focused on reacting fast but not especially accurate, which is in line with evolutionary explanations for an emotion-attention interaction. Happy faces induce a mode of processing focusing less on speed and more on evaluation of the surrounding stimuli, as is predicted by Frederickson's (Fredrickson, 1998) broadening hypothesis. From an evolutionary perspective it is sensible to increase processing only after a signal that something important is about to happen (such as angry or happy faces) when sustained attention gets less efficient due to fatigue effects.

There are some limitations to the current study. We used faces because they are strong and fast inducers of emotion and are important for social cognition but this means that the emotional effects presented here, are not generalizable to other types of emotional stimuli. It is possible that displaying an angry expression leads to considerably more distortion of facial features than a happy expression, making the sex judgment more difficult in the angry trials, which could account for some of the difference between angry and neutral faces in the short ISI condition instead of a pure valence affect. However, there was no effect for angry faces in the long ISI condition, which used the same stimuli with the same presentation time. Furthermore, Sato and colleagues (2001) also used a task that required participants to make a sex judgment for faces that showed different emotional expressions and found no correlation between sex judgment and facial expression. Finally, although we excluded participants with any psychiatric disorder, we did not measure anxiety in this study. Given that anxiety usually is correlated with a stronger interaction between emotion and attention (Fox et al., 2002), it is possible that the presented differences are based on a subgroup of more anxious participants.

Our results show that a general effect of emotion on sustained attention is that it improves reaction time. The effect of facial expressions on accuracy however, is emotion specific; accuracy decreases after negative, but not after positive cue faces. These emotion effects on probe perception are short lasting; they were only present in the short ISI condition. Future research possibilities include other types of emotional stimuli or focusing on the effect of emotion on sustained attention in psychiatric patient groups with established attentional (ADHD) and emotional (schizophrenia, depression) deficits.

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Chapter 3

Intact emotional attention modulation despite general attentional impairment in recent onset schizophrenia

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Abstract

Attentional impairments are core deficits in schizophrenia and especially sustained attention is correlated with functional outcome. Patients suffering from schizophrenia suffer from emotional deficits, especially a reduced ability to classify emotional facial expressions. The aim of the present study was to investigate, whether sustained attention is influenced differently by facial emotion as a task irrelevant stimulus property in recent onset schizophrenia patients (ROS). We used an Emotional Continuous Performance Task (E-CPT) task in which positive, negative and neutral facial expressions were used as task irrelevant cues to study the influence of negative and positive emotion on sustained attention. We compared the performance between ROS (52 males, mean age 23.3 years) and healthy controls (HC) (38 males, mean age 23.1 years). We found reduced accuracy when cues displayed a negative facial expression compared to neutral and positive expressions in both ROS and HC. Furthermore, this effect was not correlated with clinical variables. Thus, emotional modulation of sustained attention is preserved in ROS.

Introduction

Attentional impairments are core cognitive deficits in schizophrenia (Fioravanti, Bianchi, & Cinti, 2012; Heinrichs & Zakzanis, 1998). Deficits in sustained attention (vigilance), the ability to remain vigilant over a prolonged period of time, are especially important because they relate closely to functional outcome in schizophrenia (Green, Kern, Braff, & Mintz, 2000) in both early psychosis patients (Williams et al., 2008) and chronic schizophrenia patients (Prouteau et al., 2004). There is however some discussion about the stability of deficits in sustained attention over the course of the disease (Irani et al., 2011; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009).

Another factor influencing social functioning in schizophrenia is emotion processing (Kee, Green, Mintz, & Brekke, 2003; Kohler & Martin, 2006). Although the experience of affective stimuli appears to be intact in patients with schizophrenia (Hempel et al., 2005; Herbener, Song, Khine, & Sweeney, 2008), most patients report anhedonia (Burbridge & Barch, 2007) and have difficulties when anticipating future pleasurable experiences (Kring & Caponigro, 2010). The processing of emotional expressions of human faces is less efficient in patients with schizophrenia (SC) than in healthy controls (HC) (Kohler, Walker, Martin, Healey, & Moberg, 2010; Morris, Weickert, & Loughland, 2009). This deficit is not attributable to a deficit in general cognition (Goghari, Macdonald, & Sponheim, 2010) and increases with illness duration (Mueser, Penn, Blanchard, & Bellack, 1997). SC are impaired in using facial cues for social judgment (Marwick & Hall, 2008) and these disturbances are often accompanied by reduced facial expressions in SC themselves (Mandal, Pandey, & Prasad, 1998). Deficits in processing facial emotions appear to be more distinct for negative emotions in most but not all studies (Bediou et al., 2005; Tsoi et al., 2008).

In addition to the attentional and emotional disturbances, patients with schizophrenia also appear to have disturbances in the integration of emotion and cognition (Becerril & Barch, 2010; Herbener et al., 2008). At the neural level cognitive and emotional impairments even share important pathophysiological features, such that disruptions caused by schizophrenia can affect both processes and the interaction between these processes (Anticevic & Corlett, 2012). Although the literature on the interaction between emotion and attention in schizophrenia has grown rapidly in recent years (e.g. Anticevic, Repovs, & Barch, 2011; Dichter, Bellion, Casp, & Belger, 2010), there remains uncertainty about the reciprocal influence of emotion and attention in early psychosis patients.
Implicit emotion recognition and face perception depend on sustained attention, working memory capacity and speed of processing to work optimally in HC (Mathersul et al., 2009). Furthermore, emotion recognition and emotion processing are influenced by age (optimal performance between 20 and 40 years) and gender (faster explicit emotion identification and enhanced threat processing in females). In HC, higher

amounts of schizotypy scores personality features are correlated with interference from negative but not positive words on an emotional Stroop task (Mohanty et al., 2008).

In SC attentional difficulties are also correlated with deficits in facial affect recognition (Combs & Gouvier, 2004). When measured separately, an association between (sustained) attention en emotional face processing has been demonstrated (Addington & Addington, 1998), but not between attention and anhedonia or affective flattening (Berenbaum, Kerns, Vernon, & Gomez, 2008). Emotion processing and identity processing interact and the ability to attend to only one of these dimensions depends on high level processing. This process appears to be disturbed in SC with prominent negative symptoms (Baudouin, Martin, Tiberghien, Verlut, & Franck, 2002).

Strauss et al. (Strauss, Allen, Duke, Ross, & Schwartz, 2008) suggest that "impaired automatic processing may be core to diminished emotional experience" in deficit syndrome schizophrenia patients, since they found less interference from emotional words on an emotional Stroop task in deficit syndrome patients compared to non-deficit syndrome patients and HC. This is in line with other reports that only found attentional deficits for negative stimuli in SC with depressed mood (Waters, Badcock, & Maybery, 2006) or in SC with more severe negative symptoms (Strauss, Llerena, & Gold, 2011). Others found no behavioral difference in the degree of interference from emotional stimuli in SC compared to HC (Demily et al., 2009).

One possibility to measure sustained attention in SC is the AX-Continuous Performance Task (AX-CPT), in which participants view a stream of letters and have to respond to the letter X, but only when it is preceded by an A. Park et al. (Park, Kim, Kim, Kim, & Lee, 2011) presented the letters of the AX-CPT on the background of emotional faces. Their results suggest that in HC performance was not affected by background emotions and in their chronically ill patients performance was only affected by positive and not negative faces. In a follow-up experiment they demonstrated that this effect also depends on how strong the letters contrast with the background faces (Park et al., 2012). Although emotion has been used as a distracter for attention tasks, as far as we are aware, no study has investigated the effect of emotion as an intrinsic stimulus property on attention.

The aim of the present study was to investigate, whether sustained attention is influenced differently by facial emotion as a task irrelevant stimulus property in recent onset schizophrenia patients (ROS) compared to healthy controls. A secondary aim was to investigate how long a possible effect of emotion on attention is present. We used an AX-CPT with positive, neutral and negative faces instead of letters as stimuli, which is a more ecological valid way of incorporating emotion in an AX-CPT. If facial emotion recognition in ROS were impaired, we would expect that ROS would experience relatively less interference from positive and negative faces than HC. We predicted that overall performance in ROS

would be less accurate and slower than in HC. To see which (clinical) factors influence a possible interaction between sustained attention and facial expression, we not only measured positive and negative symptoms but also subjective well-being and non-verbal intelligence.

Methods

Participants

Fifty-seven male patients with recent onset schizophrenia were recruited at the Department of Psychiatry of the Erasmus Medical Centre in Rotterdam, the Netherlands. Patients were diagnosed by two senior psychiatrists and diagnoses were confirmed by the Structured Clinical Interview for DSM-IV Axis I (SCID-I) (First, 2002). Inclusion criteria were: age between 18 and 35 years and the maximum duration of illness (DoI) was five years, counting from the onset of the first positive or negative symptoms. Exclusion criteria were: any other psychiatric disorder, including substance related disorder; any neurological disease; mental retardation; use of more than one anti-psychotic drug; uncorrected vision problems. Four participants were excluded for not meeting criteria for schizophrenia at time of testing or after six months of follow up, one participant was excluded due to technical difficulties, leaving 52 ROS for the analysis.

Thirty-nine healthy male controls were recruited through advertisements on internet and word-of-mouth referrals. Additional exclusion criteria for HC were: any history of psychiatric illness in themselves or in first-degree relatives. One participant was excluded for loss of consciousness for more than 15 minutes in the medical history, leaving 38 HC for the analysis.

The Edinburgh Handedness Inventory (EHI) (Oldfield, 1971) was used to assess handedness and we used the raw scores of the Raven standard progressive matrices (Raven, 2006) to assess current general intelligence. In ROS, positive symptoms were rated with the SAPS (Andreasen, 1984) and negative symptoms with the SANS (Andreasen, 1983). The total PANSS score (Kay, Fiszbein, & Opler, 1987) was used to rate overall symptoms of schizophrenia. Overall functioning was assessed with the CAN (Slade, Phelan, Thornicroft, & Parkman, 1996). Extra pyramidal side effects of medication were evaluated with the ESRS (Chouinard & Margolese, 2005) and subjective well-being with the SWN (de Haan, Weisfelt, Dingemans, Linszen, & Wouters, 2002).

This study was part of a larger project investigating the interaction between emotion and cognition in ROS (see also chapter 6), which included several cognitive tasks, assessments and interviews over two consecutive days. The tasks described here were performed on the first day of testing. Participants received a monetary reward of 25€ for participating, regardless of performance. All participants gave informed consent and the study was conducted in compliance with the Helsinki Declaration and the regulations regarding Good Clinical Practice in the European Community (GCP) and

in concordance with the current National Regulations. The protocol was reviewed and approved by the local Medical Ethical Committee.

Task

Our CPT was adapted from the AX-CPT used by Cohen et al. (Cohen, Barch, Carter, & Servan-Schreiber, 1999) in which participants view a series of letters and have to react to a specific probe letter, but only when it is preceded by a specific cue letter. For the emotional version of the CPT (E-CPT), we replaced the letters with black-and-white portrait photos from the NimStim Face Stimulus Set (www.macbrain.org, 2009) (figure 1).

Participants were seated in a well-lit properly isolated room at approximately 60 cm distance from the 48 cm computer screen where stimuli were presented. Photos were resized to a size of 9.5° horizontally and 14° vertically. Tasks were programmed with "Presentation" 13.1 (Neurobehavioral Systems).

Participants viewed a series of faces presented sequentially on a black computer screen. They were instructed to respond to a specific probe face, but only when it was preceded by a cue face of the opposite gender. Same gender faces were used as distracter cues. Thus, participants had to remember the cues until they analyzed the probe (Riccio, Reynolds, Lowe, & Moore, 2002). Subjects were instructed to respond as accurately as possible first en as fast as possible second. Participants responded by clicking the left mouse button with their right index finger. Because all left-handed participants used their right hand to control the mouse in everyday life, they also used their right hand in this experiment.

All probe-faces displayed neutral expressions. To investigate the influence of emotion as a task irrelevant stimulus property on attention, the cue faces displayed neutral, negative (angry) or positive (happy) expressions.

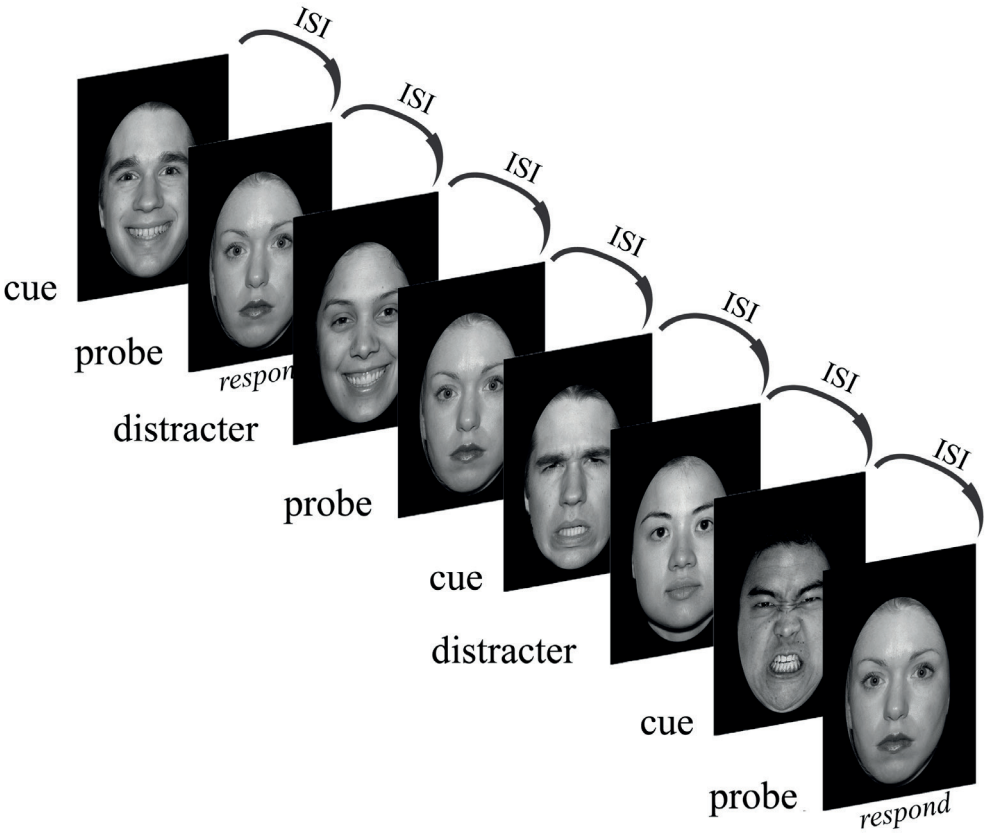
We used photos of European-American actors without facial hair. Hairstyle and clothing were removed, so gender discrimination was based only on facial features. All stimuli were presented for 500ms and response time was 1000ms, starting at the onset of stimulus presentation. Similar to Cohen et al. (Cohen et al., 1999), the ratio of target to non-target events was: 70% vs. 30%.

To investigate if differences in the duration between cue and target influences performance we varied the interstimulus interval (ISI) (figure 1). In the short condition the ISI was 500ms, in the long condition the ISI was 5000ms. All participants performed an E-CPT with short ISIs and an E-CPT with long ISIs.

To control for gender effects we used two version of the task. Half of the participants performed E-CPTs, where the correct probe was a specific female face and the correct cues were male. For the other half of the participants the correct probe was a specific male face and the correct cues were female faces. Before each task participants performed a short practice trial to get accustomed to the response buttons and trial design.

The E-CPT was administered at the end of a two hour testing session on the first day of a larger two day study investigating the influence of emotion on cognition in early psychosis patients.

Figure 1: Schematic representation of the Emotional Continuous Performance Task.



Schematic representation of the E-CPT. ISI: Interstimulus Interval. Participants were instructed to respond to a specific female probe face, but only when it was preceded by a male face. Note that the photos used in figure 1 are not the actual stimuli used in the experiment in accordance with publication restrictions of the Research Network on Early Experience and Brain Development. We used modified photographs of models 1, 2, 3, 6, 8, 9, 20, 24, 27, 30, 33 and 37 from the NimStim database.

Statistical analysis

Signal detection models were used to analyze the data. For accuracy we calculated the A-prime-score (A') (Stanislaw & Todorov, 1999). A' is a measure often used in single detection theory (Tsoi et al., 2008) and is a more specific measure of overall accuracy than hit rate (H) (Snodgrass & Corwin, 1988), since it takes into account the percentage of false alarms (FA). The formula for A-prime is: 0.5+((H-F)(1+H-F))/(4H(1-F)) when H≥F, and 0.5-((F-H)(1+F-H))/(4F(1-H)) when H<F. An A' value of 1 means 100% correct hits and no false alarms, a value of 0.5 means performance at chance level. Reaction Times (RT) were analyzed only for correct trials and furthermore trials with a RT more than 3 standard deviations from the individual mean were excluded from analysis.

We analyzed A' values and RT with mixed-model repeated measurement (RM) ANOVAs to investigate possible group differences in the influence of emotion on performance. Emotion (neutral, negative and positive) and ISI (short, long) were the within-subject variables and group (ROS, HC) the between-subjects factor. Significant effects ($p < .05$, Greenhouse-Geisser corrected) were further evaluated with post hoc t-tests. We used ANCOVAs with Raven score as covariate to evaluate the effect of IQ on emotion-attention interactions. Raw scores for the Raven standard progressive matrices were centered, to correct for large sum-of-squared errors resulting from the addition of this measure as a covariate in the analyses (Delaney & Maxwell, 1981). We used the individuals mean minus the mean of all participants method to ensure that the mean of the covariate was zero (Delaney & Maxwell, 1981; Thomas et al., 2009).

To investigate the influence of clinical variables on the effect of emotions on attention, we calculated Pearson correlation coefficients for the difference between neutral and either positive or negative scores and the clinical variable scores. Data were analyzed with SPSS version 21 (IBM 2012).

Results

Demographic data and group comparisons

There was no difference in age or handedness between groups (see table 1). On average, ROS scored lower on the Raven than HC (HC 51.9, ROS 46.2, $t(88)= 3.252$, $p = .002$) and the percentage of Caucasian participants was higher in the HC group (67.6% vs 44.2%, Fisher Exact $p = . 032$).

Accuracy

The omnibus mixed model RM-ANOVA with emotion (neutral, negative and positive) and ISI (short, long) as within-subject variables and group (HC, ROS) as between-subjects factor for A' values (see table 2) revealed a main effect for group ($F(1,89) = 12.722$, $p = 0.001$, $\eta 2 = 0.126$), indicating that overall accuracy in ROS (0.923) was lower than in HC (0.957, $t(77.7)= 3.900$, $p < .001$). We also found a main effect for

Table 1: Demographic and clinical variables

	Patients with Schizophrenia		Healthy Controls		t-test
	Mean	SD	Mean	SD	
n	52		38		
Age (years)	23.3	4.3	23.1	4.3	n.s.
Caucasian (%)	23 (44%)		26 (67%)		p = .032*
Left Handed (%)	5 (10%)		4 (11%)		n.s.*
Raven score	46.2	8.7	51.9	7.6	p = .002
Duration of Illness (months)	20.6	17.9			
SANS	39.7	21.6			
SAPS	19.3	15.3			
PANSS total	59.4	15.3			
SWN	84.4	15.7			
Medication Free	13 (25.0%)				
CPZ equivalent**	259.6 mg	160.7 mg			
ESRS	6.2	6.8			

**: Fisher exact, **: only for patients taking medication, n = 39*
Abbreviations: PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SWN, Subjective Well-Being Under Neuroleptics scale, CPZ equivalent, Chlorpromazine equivalents; ESRS, Extrapyramidal Symptom Rating Scale.

ISI ($F(1,89) = 59.520$, $p < 0.001$, $\eta 2 = 0.403$), post hoc t-tests revealed that accuracy was lower in the short than the long ISI condition (0.919 vs 0.957, $t(89) = -8.010$, $p < .001$). There was a main effect for emotion ($F(2,88) = 3.842$, $p = 0.024$, $\eta 2 = 0.042$). Accuracy for negative facial cues (.933) was lower than for positive (.940, $t(89) = 2.770$, $p = .007$) and neutral facial cues (.939, $t(89) = -2.172$, $p = .033$).

The group by emotion interaction was not significant, but the group by ISI interaction reached significance ($F(1,89) = 4.076$, $p = 0.047$, $\eta 2 = 0.044$), caused by a larger difference in accuracy at the short compared to the long ISI condition in ROS than HC. There was no group by emotion by ISI interaction. The interaction between emotion and ISI was significant ($F(2,88) = 5.841$, $p = 0.005$, $\eta 2 = 0.062$). Accuracy for positive cues decreased less between the two ISIs than for negative and neutral cues.

Since groups differed on Raven score and general intelligence is correlated with performance on attention tasks, we included the (centered) Raven scores as covariate. The main effects of group, emotion and ISI remained significant, as well as the emotion by ISI interaction.

Based on a study in healthy controls (chapter 2), we analyzed the accuracy data for the short and the long ISI separately with a mixed-model RM-ANOVA with emotion (neutral, negative and positive) as within-subject variable and group (HC, ROS) as between-subjects factor. For the short ISI data, we found a main effect for group ($F(1,89) = 11.164$, $p = 0.001$, $\eta 2 = 0.113$) and a main effect for emotion ($F(2,88) = 9.041$, $p < 0.001$, $\eta 2 = 0.093$); performance on positive trials (A' 0.93) was better than on neutral (A' 0.92, p=.006, t=2.830) and negative trials (A' 0.91, p<.001, t=4.692) while there was no difference in performance between neutral and negative trials. However, we found no group by emotion interaction. For the long ISI data, we found a main effect for group ($F(1,89) = 10.435$, $p = 0.002$, $\eta 2 = 0.106$) but no main effect for emotion and no group by emotion interaction.

Table 2: accuracy (A') and Reaction Time (RT) for the different emotional conditions

		Patients with Schizophrenia		*Healthy Controls*		*t-test*
A'		*Mean*	*SD*	*Mean*	*SD*	
ISI short	*Negative*	*.891*	*.073*	*.935*	*.041*	*p < .001*
	Neutral	*.896*	*.092*	*.947*	*.043*	*p = .001*
	Positive	*.911*	*.071*	*.950*	*.042*	*p = .004*
ISI long	*Negative*	*.945*	*.062*	*.971*	*.027*	*p = .009*
	Neutral	*.951*	*.048*	*.974*	*.034*	*p = .010*
	Positive	*.942*	*.043*	*.968*	*.025*	*p = .001*
RT (ms)		*Mean*	*SD*	*Mean*	*SD*	
ISI short	*Negative*	*399*	*76*	*359*	*42*	*p = .002*
	Neutral	*411*	*80*	*367*	*48*	*p = .002*
	Positive	*410*	*93*	*356*	*43*	*p < .001*
ISI long	*Negative*	*565*	*308*	*424*	*82*	*p = .002*
	Neutral	*543*	*277*	*421*	*79*	*p = .004*
	Positive	*550*	*297*	*412*	*68*	*p = .002*

Reaction Time

We analyzed RT (see table 2) in the same way as accuracy. Again, there was a main effect for group ($F(1,89) = 9.411$, $p = 0.003$, $\eta 2 = 0.097$), indicating that overall reaction time in ROS (479 ms) was slower than in HC (390 ms, $t(62.5)= 3.501$, $p = .001$). We found a main effect for ISI ($F(1,89) = 24.518$, $p < 0.001$, $\eta 2 = 0.218$), post hoc t-tests revealed that reaction time was slower in the long than in the short ISI condition (496 ms vs 388 ms, $t(89)= 5.293$, $p < .001$). The main effect for emotion was not significant.

The emotion by group interaction for was not significant. The interaction between group and ISI was significant ($F(1,89) = 4.540$, $p = 0.036$, $\eta 2 = 0.049$). ROS had larger differences of RT between the short and the long ISI condition than HC (144ms vs 58 ms). There was no group by emotion by ISI interaction. The interaction between emotion and ISI was significant ($F(2,88) = 7.089$, $p = 0.002$, $\eta 2 = 0.075$). Negative faces had a facilitating effect in the short ISI condition, but an interference effect in the long ISI condition, both compared to the RT with neutral cues.

When we included the Raven scores as covariate, the main effects of group and ISI remained significant, the group by ISI interaction no longer reached significance. The interaction between emotion and ISI also remained significant.

Analyzing the RTs for the short ISI separately, we found significant main effects for group ($F(1,89) = 10.064$, $p = 0.002$, $\eta 2 = 0.103$) and for emotion ($F(2,88) = 5.658$, $p = 0.005$, $\eta 2 = 0.060$); reactions time was faster for negative (382 ms) than neutral trials (392, $p=.002$), but both did not differ from positive trials (387ms). We also found a trend level interaction between emotion and group ($F(2,88) = 2.698$, $p = 0.073$, $\eta 2 = 0.030$). In the long ISI condition, only the main effect for group reached significance ($F(1,89) = 7.591$, $p = 0.007$, $\eta 2 = 0.079$).

Clinical variables

For both reaction time and accuracy, the effect of negative or positive faces was not correlated with: duration of illness; SANS score; SAPS score; PANSS total score; ESRS; SWN; or CPZ equivalent.

Discussion

This study was designed to investigate whether the influence of emotion, as a task irrelevant stimulus property, on sustained attention is reduced in recent onset schizophrenia patients. We used an adapted AX-CPT where instead of letters faces displaying positive, neutral and negative facial expressions were used as stimuli. We confirmed the results from our previous study (**chapter 2**). Accuracy was reduced when cues displayed a negative emotional expression. As predicted, there was a general attentional deficit in ROS, they were less accurate and reacted more slowly than HC. In contrast to our hypothesis, ROS had the same influence of faces with negative emotional expression on sustained attention as HC. Thus, we found no evidence that emotional modulation of

sustained attention is impaired in male ROS. Furthermore, emotion effects were not correlated with clinical variables.

Park et al. (2011) also used an adapted AX-CPT to investigate the influence of emotion on sustained attention in patients suffering from schizophrenia. Numbers instead of letters were used as stimuli and they were presented against a background of pictures showing facial expressions (happy, neutral or sad) over three experimental blocks for each emotion. Patients had a stronger decrease of attention over time than healthy controls, and this impairment of sustained attention was significantly more prominent in the happy face condition compared to the neutral and sad face condition. In HC accuracy was not affected by facial expressions, which implies that the effect of facial expressions is stronger in patients then HC. Although this finding differs from our results, Park et al. (2011) note two important limitations for their study. Firstly, they did not find a significant three-way interaction between group, emotion and time. Secondly, there might have been a ceiling effect in HC which could have obscured the effect of emotion. Our study did show an emotion effect in HC and this effect did not differ in patients. An explanation for our results could be that despite impairments in facial emotion perception in SC (Kohler et al., 2010), the priming of facial emotion perception by negative emotions is still intact in SC (Hoschel & Irle, 2001). This means that HC and SC judge a neutral facial expression as significantly more negative when it is preceded by a negative emotional facial expression compared to when it is preceded by a positive or neutral emotional facial expression (Hoschel & Irle, 2001).

Other studies investigated correlations between AX-CPT performance and emotion discrimination tasks. Chung et al.(Chung, Mathews, & Barch, 2010) found no correlation between AX-CPT performance and emotion perception in SC. They did find a positive correlation between AX-CPT performance and measures for social cognition in SC, which is in line with the results described in **chapter 7**. They concluded that problems with integrating (emotional) context information are a key component of impaired social inference in schizophrenia. However, this study did not investigate the effect of emotion on sustained attention, measured with the AX-CPT, but used a correlational approach. In addition the study aimed to answer the question to what extent impairments of context processing might impair emotion recognition in patients with schizophrenia. When looking at our results from a context processing point of view, changing the context from neutral (neutral cue faces) to emotional (happy or angry cue faces) had the same effect on performance in SC and HC. This means that the subconscious integration of emotion and context processing would (still) be intact, at least in ROS. This is in line with our results on emotional memory modulation in recent onset schizophrenia (**chapter 6**), where we also found a general cognitive deficit, but intact modulation of cognition by emotion in ROS. With our study design, no conclusion can be drawn, whether emotion recognition was impaired in the participants with schizophrenia compared to healthy controls.

Addington and Addington (1998) did find an association between sustained attention and facial affect recognition in SC which was not present in HC. Combs and Gouvier (2004) showed that in SC attention is significantly predictive of affect perception scores while psychiatric symptoms, medication levels, demographic variables, and face recognition scores were not. They used a four factor model of attention and found that the "Shift" factor had the highest predictive value followed by "Encode" and "Focus-Execute" factors while the "Sustain" factor had the least predictive value (Combs & Gouvier, 2004). So, it is possible that we would have found impaired emotional modulation if we had investigated a different subdomain of attention, yet the study in **chapter 4** investigated the influence of emotion on selective attention and there was also no impaired emotional modulation. When looking at these correlational studies, it is important to take into account that in an explicit facial affect recognition task participants have to study a face, recognize the emotion, translate it into a word and provide that answer. Lower scores for SC on these tasks could represent an impairment in recognizing the expression, but also an impairment in translating a correctly recognized emotion into the correct answer. If the latter is the case in ROS, then implicit effects of emotion could still be intact, as in our study, while they score lower on facial affect recognition tasks.

Several others studies investigated the interaction between attention and emotion in more chronic schizophrenia patients using functional MRI. Despite intact task performance, these studies found evidence for either disturbances in the interaction between frontal and limbic brain regions (Dichter et al., 2010) or between prefrontal brain regions and the amygdala (Anticevic et al., 2011) in SC. This means that although the ROS in our study did not show any deficits in the modulation of attention by emotion, it is possible that there are already subtle disturbances in the interaction between "emotional" and "cognitive" brain regions.

Our results are in line with studies that investigated the emotional modulation of the startle response; although these studies seem to show a general deficits in SC, SC respond appropriately to emotional stimuli at the behavioral and physiological level (Kring & Moran, 2008). Linden et al.(2010) investigated the influence of emotional faces on working memory and also found that although there is a general working memory deficit and an emotion effect (angry face benefit), there was no group by emotion interaction.

There are some limitations to our study. First of all, to keep the duration and burden of the task acceptable, we did not include fearful faces as a fourth category of stimuli. Some studies have reported that the interaction between cognition and facial expressions is stronger for fearful than happy or sad faces (e.g. Wout van ‘t et al., 2007). It is possible that we would have found an emotion by sustained attention interaction if we had used fearful faces. We investigated male ROS patients for several reasons. The investigation of ROS eliminates the possible confounders of chronic illness and chronic use of medication. Because it has been shown

in HC that emotion recognition depends on age and gender (Mathersul et al., 2009), a small age range reduces variance. Although this reduces the influence of confounding factors, it also makes our results less generalizable to patients suffering from schizophrenia in general.

Conclusion

We investigated whether sustained attention is influenced differently by facial emotion as a task irrelevant stimulus property in recent onset schizophrenia and found that ROS were less accurate and slower than HC. However, the effect of emotion, a negativity bias, was the same in ROS as in HC and was not correlated with clinical variables. These results are in line with previous studies that investigated the effects of emotion on attention in schizophrenia and expand these results to recent onset schizophrenia patients.

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Chapter 4

Effects of emotional words on selective attention in patients with recent onset schizophrenia

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in preparation for submission

Abstract

In patients with schizophrenia, an impairment of selective attention has been repeatedly described, also in the early course of the disease. The Stroop-task is one way to investigate selective attention by presenting colour word written in letters of the same or a different colour with the task to ignore the irrelevant word content and react on the colour of the letters. Here we investigated to what extent emotional word content influences focused attention in 30 patients with recent-onset schizophrenia compared to 26 healthy controls. Next to the standard Stroop-task participants performed an emotional version of the Stroop task with negative, neutral and positive words. All word categories were presented intermixed in a pseudo-randomized order. As expected, patients responded slower to all stimuli. Negative words caused increased RT compared to neutral and positive words in all participants However, there was no interaction between the group and the word categories, neither when all, nor when only the emotional categories were analysed. These results suggest that in patients with recent onset schizophrenia the impact of emotion on selective attention is still intact with respect to verbal stimuli.

Introduction

Although DSM-IV, DSM-V and the ICD-10 define schizophrenia by the presence of disorganisation, psychotic and negative symptoms, early psychiatrists such as a Kraepelin (1899) and Bleuler (1916) judged cognitive and emotional disturbances as the core features of schizophrenia. Indeed, with respect to functional and occupational outcome of patients with schizophrenia, impairments in cognitive (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006; Szoke et al., 2008) and emotional (Kring & Moran, 2008; Strauss & Herbener, 2011) functions seems to be more relevant than psychotic or negative symptoms by itself (Gonzalez-Blanch et al., 2008).

In general, patients with schizophrenia are impaired when tested on different domains of higher cognitive functions, such as sustained (Hahn et al., 2012), selective (Nuechterlein, Pashler, & Subotnik, 2006) and spatial attention (Suslow, Roestel, Ohrmann, & Arolt, 2003), executive function (Krieger et al., 2005), working memory (Barch, 2006), language (Stephane, Pellizzer, Fletcher, & McClannahan, 2007), explicit and implicit learning (Pedersen et al., 2008) and memory (Leavitt & Goldberg, 2009). With respect to emotional impairments in patients with schizophrenia, contradictory results have been reported. Many studies have reported that patients with schizophrenia recognise facial emotional expressions less accurately than healthy controls (Kohler et al., 2003), especially when faces display negative emotions such as anger or fear (Scholten, Aleman, Montagne, & Kahn, 2005). However, patients with schizophrenia do not differ in their subjective evaluation of visual emotional stimuli (Hempel et al., 2005; Pinheiro et al., 2013) such as pictures from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2001). Similar results have been described for words with emotional content (Jalenques, Enjolras, & Izaute, 2013).

Selective attention, the ability to process a relevant stimulus while ignoring irrelevant environmental stimuli, is one of the cognitive functions that is impaired in patients with schizophrenia (Nuechterlein et al., 2006). A widely used test to examine selective attention is the Colour-Word-Stroop-Task. In the original card version (Stroop, 1935), a card with a number or words in different colours is presented to the participants. Participants are asked to read aloud the ink-colour, in which the words are written, while ignoring the word-content. Words may be a colour name, congruent or incongruent to the ink-colour, or any other word. Computerized versions use a single-trial design and may use designated buttons to identify the colour. While a recent meta-analysis (Westerhausen, Kompus, & Hugdahl, 2011) concluded that patients with schizophrenia show a stronger increase in reaction time for incongruent colour-words compared to neutral words (interference) than healthy controls, another review (Henik & Salo, 2004) reported divergent results in patients with schizophrenia; augmented interference in the card version and augmented facilitation, but no augmented interference in the single trial version. In healthy controls, many studies have shown that mood induction or the

emotional content of stimuli may influence cognitive abilities. A recent review (Lench, Flores, & Bench, 2011) has shown that performance in cognitive tasks was modulated by mood-induction prior to the experiment by film clips, imagination, music, pictures and verbal stimuli, both compared to neutral and between different types of mood (happiness, anger, anxiety). However, the effect of the different emotions varies and cognitive functions are differentially affected by mood-induction (Martin & Kerns, 2011).

With respect to the influence of emotional stimuli on attention studies report contradictory results. For certain classes of stimuli, such as faces and pictures, it seems that they are evaluated for their emotional meaning (Compton, 2003) very early and therefor have the ability to grasp attentional resources very early. In contrast, emotional words seem to attract more attention only when their semantic features have to be discriminated (Hinojosa, Mendez-Bertolo, & Pozo, 2010), which is associated with differences in late positive components of event-related brain potentials (ERPs). Threatening schematic faces were detected faster than faces with a neutral or happy expression (Ohman, Lundqvist, & Esteves, 2001), but photographs of human faces with happy expressions were detected faster and with higher accuracy (Juth, Lundqvist, Karlsson, & Ohman, 2005) than faces with angry or fearful expression.

With the emotional Stroop-task in healthy participants again diverging results are reported; no effects of emotional words (Franken, Gootjes, & van Strien, 2009) on the one hand, and increased reaction times of negative (Gootjes, Coppens, Zwaan, Franken, & Van Strien, 2011) or taboo words (Bertels, Kolinsky, Pietrons, & Morais, 2011) compared to neutral words on the other hand. However, study design, especially mixed versus blocked presentation of word categories, seems to be of major relevance (Phaf & Kan, 2007; Waters, Sayette, Franken, & Schwartz, 2005), with stronger effects of emotion in the blocked presentation version.

Similar to healthy controls, in patients with schizophrenia emotion seems to affect attention (Besnier et al., 2011; Demily et al., 2010; Dichter, Bellion, Casp, & Belger, 2010; Phillips, Deldin, Voglmaier, & Rabbit, 2005; Strauss, Allen, Duke, Ross, & Schwartz, 2008), but also other cognitive functions such as memory (Becerril & Barch, 2011; Herbener, 2008). Several studies have examined the influence of emotion on selective attention in patients with schizophrenia or delusional disorder with the emotional Stroop test. Some of them used the card-version (Bentall & Kaney, 1989; Besnier et al., 2011; Kinderman, 1994) and compared them to healthy controls. All of these studies examined in addition a group of patients with affective disorder. Others used a computer-based single trial version (Demily et al., 2010; Phillips et al., 2005; Strauss et al., 2008). Bentall and Kaney (1989) presented in one condition words with potentially threat-related content and in the other words with depressive content. They reported a significantly higher effect of interference for deluded patients for threat related words compared to both control groups. Besnier et al. (2011) used words with paranoid, depressive and manic

content. Patients with schizophrenia had significantly increased RT in the paranoid condition compared to the neutral and manic condition, while bipolar patients had increased RT in the manic and depressive compared to the neutral and paranoid condition. In contrast, healthy controls had no differences in RT between word categories. Kinderman (1994) used personally descriptive adjectives with negative or positive content. He found stronger interference for positive and negative adjectives in both patient groups compared to healthy controls. Although deluded patients had significantly higher total interference scores than depressed patients, effects for word types were similar in both groups as shown by the lack of group by word interaction.

The emotional Stroop task single trial studies examined patients with chronic schizophrenia only (Demily et al., 2010; Phillips et al., 2005; Strauss et al., 2008). Phillips et al. (2005) reported interference for negative and facilitation for positive words for both patients and healthy controls. Patients and healthy controls did not differ, not even in absolute reaction times and accuracy. Disorganization in patients increased the effects of emotion; stronger interference for negative and stronger facilitation for positive words. Strauss et al. (2008) used five different word categories. In contrast to the previous study, patients showed more interference than healthy controls. In patients with deficit syndrome, happy words facilitate reaction times compared to healthy controls and patients without deficit syndrome. In the study of Demily et al. (2010) positive and negative words caused interference in patients and healthy controls, without a significant group by word interaction, but overall increased reaction times in patients.

An fMRI-study (I. H. Park, Park, Chun, Kim, & Kim, 2008) with an adapted Stroop-task, using pictures combined with congruent and incongruent emotional words found no differences in reaction time (RT) between patients with schizophrenia and healthy controls for both congruent and incongruent trials. On fMRI-level a different pattern of BOLD-signal changes was found in the subgenual anterior cingulate gyrus, that is, a reduction during incongruent trials in healthy controls, but not in the patient group. To sum up the results of the presented studies remain inconclusive with respect to the question whether emotional modulation of selective attention differs between healthy controls and patients with schizophrenia.

To our knowledge, this study is the first study that used an emotional Stroop-task in patients with recent-onset schizophrenia to examine the effect of emotion on selective attention. In contrast to the earlier mentioned studies (Bentall & Kaney, 1989; Besnier et al., 2011; Demily et al., 2010; Kinderman, 1994; Phillips et al., 2005; Strauss et al., 2008), we examined patients with short illness-duration using a Stroop-task that included emotional and colour words. By examining this patient group, effects of long-term use of antipsychotics and effects of chronicity of the disorder as cofounders are reduced, giving more insight into to what extent possible impairments are already present in the early stages of the

disorder. We hypothesized, based on the existing literature, that patients would show the same magnitude of interference in the incongruent colour-word condition as healthy controls and that they would show a similar interference/facilitation effect of emotional words as healthy controls.

Methods

Participants

We studied 30 male patients (see table 1 for details) with recent-onset schizophrenia (defined as duration of illness < 5 years, age between 16 and 35 years) (mean age 23.9 years, SD=3.5, range=18-32). The median of illness duration was 17 month (range 1-50 months). All patients were or had been hospitalized in the department of psychiatry of the Erasmus MC and were diagnosed according to DSM-IV criteria. Diagnoses were made by clinical consensus and were confirmed from case-notes using OPCRIT criteria (McGuffin, Farmer, & Harvey, 1991). Patients with symptom-duration of less than 6 months were reassessed after 6 months to comply with the DSM-IV criteria. We defined beginning of schizophrenia as the occurrence of psychotic symptoms or clear limitations in social or occupational functioning if these occurred earlier. This method yields a relatively long duration of illness when compared with assessing only positive symptoms.

Current psychopathology was rated with the Positive and Negative Symptom Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) at the day after testing. The median symptom scores were: positive 12.5 (range 7-25), negative 17 (range 8–32), general 29,5 (28-49) and total 60 (39-97). Nine patients were free of antipsychotics for at least 8 weeks and 21 (SC-med) on a stable dose of medication for at least 4 weeks (see table 1) and all patients received no additional psychotropic medication. Mean dosage expressed in chlorpromazine (CPZ)-equivalents was 347 mg (SD 149 mg). Treated and untreated patients did not differ in psychopathology ratings and age. Because the group of un-medicated patients was rather small, we analysed all patients as one group compared to healthy controls.

Twenty-six age- and gender-matched healthy volunteers (HC) (mean age 24.6 years, SD=4.1, range=18-31) were selected as a control group (see table 1 for details). Groups did not differ in age ($t(54)=0.64$, $p=.56$). None of the HC met criteria for a current diagnosis or history of any axis I disorder, serious somatic disorder or any cerebral trauma. Colour blindness was tested by having participants name the colour of patches that were the same colour as the stimuli used in the Stroop-task. Because of the frequent methodological problems when trying to match SC with HC on variables such as education or intelligence (Meehl, 1970), we decided not to match HC with the two patient groups on level of education. As a consequence, SC and HC differed in level of education (HC 11.96 years, SC 10.43 years, $t(33.25)=10.44$, $p<.001$). The study was approved by the research ethics committee of Erasmus MC, Rotterdam,

and subjects gave written informed consent before participation.

Tabel 1: Demographic characteristics of participants

	Patients with Schizophrenia		Healthy Controls	
	Mean	range	Mean	range
n	30		26	
Age (years) n.s.	24	17 - 32	23.9	18 - 32
	Mean	SD	Mean	SD
Education (years) **	10.4	0.8	12	0.2
Duration of Illness (months)	18	13.5		
Medication (n=21)	CPZ-equivalent	SD		
Clozapine (n=7)	423	108		
Cyclopentixol (n=2)	275	35		
Haloperidol (n=7)	263	70		
Olanzapine (n=2)	175	107		
Quetiapine (n=2)	640			
Risperidone (n=1)	300			
medication free (n=9)				
PANSS-score	Mean	SD		
Positive	13.5	7.2		
Negative	17.8	8.7		
General	30.5	13.1		
Total	61.8	26.9		

**: p < 0.05, **: p < 0.01, ***: p < 0.001, n.s.: not significant*

Emotional Stroop-task

Participants were examined with a modified Stroop-task, previously used in an FMRI study with healthy controls (Evers, van der Veen, Jolles, Deutz, & Schmitt, 2006). A word was presented every 2 s against a black background and stayed on the screen until participants responded. In total 152 words (Font: Helvetica, letter-size 48) were presented in a pseudo-randomized order (never the same colour three times in a row) on a 20-inch computer-screen placed 60 cm in front of the subjects. Words were presented in the middle of a black screen. Word length, which varied between 3 and 6 letters, was balanced between the emotion conditions. Size of stimuli was between 5.7° and 11.4° visual angle in width and 1.9° in height. For the Stroop-task we used four colour words: blauw (blue), groen (green), rood (red) and geel (yellow) and 72 non-colour words with emotional content. Stimuli comprised 40 congruent colour-words

(letters were written in the same ink as the colour word), 40 incongruent colour-words (letters were written in a different ink as the announced colour), 24 negative, 24 positive and 24 neutral words, all written in Dutch. To overcome starting problems the test-block was preceded by 10 neutral words, which were not included in the analysis. Participants were instructed to react as fast as possible by pressing a designated key on a computer keyboard for the colour, in which the displayed word was written. Participants were instructed to keep their fingers over the keyboard in preparation to make a response. Participants received no feedback. To get accustomed to the designated keys (S for blue, D for red, K for green, L for yellow) participants performed a training session containing 40 congruent and 40 incongruent colour words and 72 neutral words not used in the consecutive trial. We used 4 different pseudo-randomized versions of the task. The task was programmed in E-Prime V1.0 (Psychology Software Tools, 2002).

Statistics

Reaction times (RT) were analysed only for correct trials for each condition and participant individually. RT higher or lower than 2 SD from the individual mean where excluded from further analysis. Data were analysed with a mixed model repeated-measurement ANOVA and t-tests where appropriate using SPSS 20. Influence of psychopathology or medication expressed in CPZ-equivalents were analysed by calculating cross-correlations (for patients only). Error probability was set at $p < .05$ (two-tailed). All tests were Greenhouse-Geisser corrected and p-values were corrected for multiple comparisons where appropriate.

Results

Reaction times

We calculated an omnibus two-factorial mixed-model repeated-measurement ANOVA with word-type as within-subject factor and group (HC, SC) as between-subject factor (see table 2 for RT values). We found a main effect for group ($F(1,54)=14.393$, $p<.001$, partial-$\eta 2=.21$) and word-type ($F(3.2,173,9)=29.995$, $p<.001$, partial-$\eta 2=.36$), but no significant interaction ($F(3.2,173,9)=2.079$, $p=.10$, partial-$\eta 2=.037$). Thus overall, patients had longer RT, but effects of word-type were the same between groups (see also figure 1).

Because we were mainly interested in the differences between the three emotional word categories we performed planned contrasts between negative and neutral words and positive and neutral words respectively. These showed a significant longer RT for negative words as compared to neutral ($t(55)=2.293$, $p=.026$) and no significant difference between positive and neutral words ($p=.891$).

In addition, we compared the mean RT pooled over all non-colour words and the mean RT of congruent (facilitation) and incongruent (interference) colour-words. There was a facilitation effect for congruent colour

words (F(1,54)=4.794, p=.033, partial-η2=.08), but no interaction between group and facilitation (F(1,54)=2.221, p=.142, partial-η2=.04). In addition, there was a significant interference effect for non-colour words (F(1,54)=63.425, p<.001, partial-η2=.54), but again no interaction between interference and group (F(1,54)=2.245, p=.139, partial-η2=.04).

Our main interest was the influence of different categories of emotional words on selective attention. The variance of the standard Stroop-task could have overruled small, but significant differences between the emotional word categories Therefore, we calculated a mixed-model repeated-measurement ANOVA for the emotional words only, with word-type as within-subjects factor and group (HC, SC) as between-subjects factor. Again, we found a main effect for group (F(1,54)=15.180, p<.001, partial-η2=.22) and word-type (F(1.9, 104.3)=3.832, p=.026, partial-η2=.06), but no significant interaction (F(1.9, 104.3)=0.830, p=.435, partial-η2=.02). Thus overall, patients had longer RT, but even now effects of emotion were the same between groups.

Comparisons between treated and untreated patients revealed no significant differences, neither in the omnibus, nor in the analysis of emotional words only. The correlation analysis in the patient group between psychopathology ratings, CPZ-equivalents, level of education and the RT for the five conditions remained all non-significant (all p's >.17).

Table 2: Mean reaction times and errors for the diferent word categories with standard deviation in ms in brackets.

	Congruent	Incongruent	Neutral	Negative	Positive
RT (ms)					
SC	908 (233)	979 (203)	911 (228)	922(182)	906 (224)
HC	685 (154)	811 (231)	700 (167)	735 (183)	709 (163)
Errors					
SC	1.1 (1.5)	2.3 (1.8)	0.1 (1.5)	0.8 (1.1)	1 (1.2)
HC	0.9 (0.8)	1.8 (1.6)	0.4 (0.6)	0.7 (0.8)	0.3 (0.6)

Error rates

We calculated an omnibus mixed-model repeated-measurement ANOVA with word-type as within-subject factor and group (HC, SC) as between-subject factor. We found only a main effect for word-type (F(2.464)=25.161, p<.001, partial-η2=.32), but no significant main effect for group or group by word-type interaction.

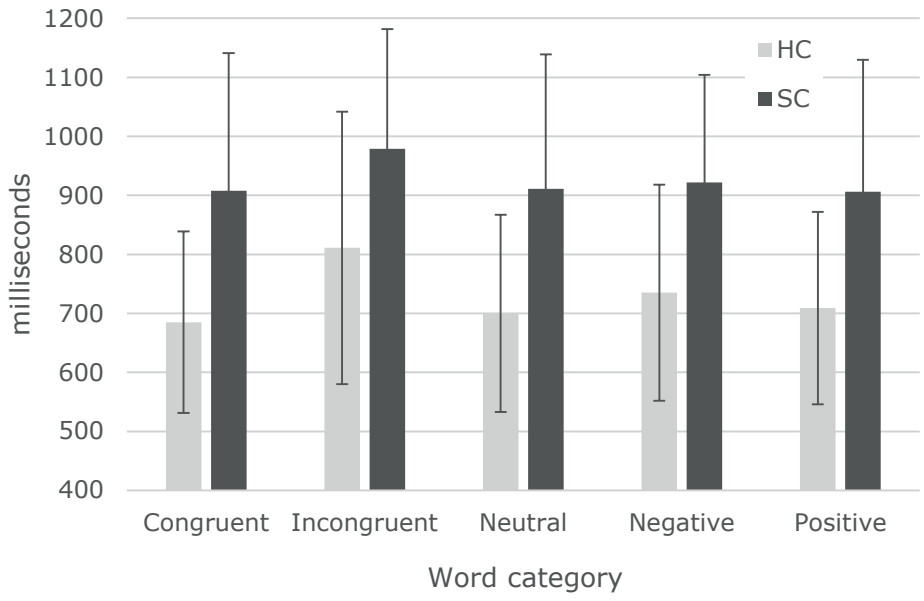
Our main interest was the effect of emotional word category on error rate, thus we performed planned contrasts between the error rates for negative, positive and neutral between the two groups. Patients with schizophrenia had significantly higher error rates for positive words (t(42,1)=2.72, p=.009), error rates for negative (p=.785) and neutral

(p=.429) words did not differ between groups.

In addition, we compared the mean error-rate pooled over all non-colour words and the mean error-rate of congruent and incongruent colour-words. There was a facilitation effect for congruent colour words ($F(1,54)=8.822$, $p=.004$, partial-$\eta 2=.14$), but no interaction between group and facilitation ($F(1,54)=0.571$, $p=.453$, partial-$\eta 2=.01$). In addition, there was a significant interference effect for non-colour words ($F(1,54)=43.817$, $p<.001$, partial-$\eta 2=.45$), but again no interaction between interference and group ($F(1,54)=0.099$, $p=.754$, partial-$\eta 2=.002$).

Finally, we calculated a mixed-model repeated-measurement ANOVA for the emotional words only, with word-type as within-subject factor and group (HC, SC) as between-subject factor. Here we found no significant main effects, but a significant interaction ($F(1.970)=3.297$, $p=.042$, partial-$\eta 2=.06$), driven by the above mentioned significantly higher error rates for positive words in patients. The correlation analysis in the patient group between psychopathology ratings, CPZ-equivalents, level of education and the error-rate for the five conditions all remained non-significant (all $p > .13$).

Figure 1: Mean reaction times with standard deviations for the different word categories.



Discussion

To our knowledge, this is the first study that used an emotional Stroop-task in patients with recent-onset schizophrenia. We found an overall increase in reaction time in patients compared to healthy controls. In both patients and healthy controls, incongruent colour words caused interference and congruent colour words caused facilitation compared to non-colour words. However, no group differences or interactions where found. Thus, interference and facilitation did not differ between groups. With regard to the emotional words, we found an interference effect for negative words as compared to neutral words but no facilitation for positive words. Again, both groups showed similar effects. Thus, patients with schizophrenia are distracted in the same way as healthy controls by the content of negative in comparison to neutral words. Both, patients and healthy controls are not affected by positive in comparison to neutral words. A slightly different result was found for errors. While for the standard Stroop-task both groups had similar error rates, patients made more errors when positive words were presented, while error rates for neutral and negative words were similar between groups.

Previous studies reported that patients with schizophrenia and healthy controls had the same amount of interference by incongruent colour words as compared to neutral words and even an increased facilitation by congruent colour words (Barch, Carter, & Cohen, 2004; Barch, Carter, Hachten, Usher, & Cohen, 1999; Henik et al., 2002; Henik & Salo, 2004). However, a recent meta-analysis reported increased interference in patients with schizophrenia (Westerhausen et al., 2011). But as Westerhausen et al. (2011) and Henik & Salo (Henik & Salo, 2004) stated, this effect is much more present in the card version than in the single-trial version. Thus, the lack of differences in interference in our study, confirms the results of the previous mentioned studies. Inconsistent results are also reported with respect to facilitation in schizophrenic patients with schizophrenia. Some reported increased facilitation in patients as compared to healthy controls (Barch, Carter, Perlstein, et al., 1999; Henik et al., 2002) others found no differences (Salo, Robertson, & Nordahl, 1996). However, most studies are performed in chronic patients. Our finding that patients and controls did not differ with respect to facilitation, are in accordance with the results of Chen et al. (2001), who examined a Stroop-task in a sample of first-episode patients with schizophrenia, which most strongly resembles our sample of recent-onset patients, except that their mean age was 10 years higher than in our sample. Remarkably, in the study of Chen et al. (2001) the subgroup of treated patients showed a facilitation effect, which disappeared at the time of retesting after 4 months. We did not find any differences between treated and untreated patients, but for a thorough statistical comparison our study was probably underpowered.

Seven studies used emotional Stroop-tasks in patients with schizophrenia (Besnier et al., 2011; Demily et al., 2010; S. Park, Puschel, Sauter, Rentsch, & Hell, 2002; Phillips et al., 2005; Strauss et al., 2008) or deluded patients (Bentall & Kaney, 1989; Kinderman, 1994). Studies

differed in some aspects from ours. Bentall & Kayne (1989), Kinderman (1994) and Besnier (2011) used card-versions of the Stroop-task. Park et al. (2002) used an adapted version with emotional word-picture (in)-congruency. Demily et al. (2010), Phillips et al. (2005) and Strauss et al. (2008) used a single-trial verbal design, but did not include the standard Stroop-task. All studies reported an interference effect for negative stimuli in patient groups, but results differed with respect to healthy controls. Studies using the card-version (Bentall & Kaney, 1989; Besnier et al., 2011; Kinderman, 1994) found increased interference for words with negative emotional content (threat-related, paranoid) in patients compared to healthy controls, and Kinderman (1994) also for positive words. Park et al. (2002) found no group differences in interference regarding RT, but for performance efficiency, patients had greater interference in the incongruent emotional word-picture condition. Strauss et al. (2008) divided the group of patients in those with and those without deficit syndrome. The three negative word categories (anger, anxiety and sadness) caused in both patient groups a similar interference effect as healthy controls. Happy words caused interference in healthy controls and non-deficit patients, but not in deficit patients.

The studies most similar to ours (Demily et al., 2010; Phillips et al., 2005) found no differences between patients and controls in any of the conditions. Both studies found an interference effect for negative words, which we also observed in our sample. Conflicting results were reported for the effect of positive words, Demily et al. (2010) report an interference effect, while Phillips et al. (2005) found no effect, similar to the observation in our sample. Importantly, our finding that all effects (cognitive and emotional Stroop-task) did not differ significantly between patients and healthy controls, are in accordance with the results of both studies. In conclusion, all studies reported emotional modulation of attention by stimuli with negative content in patients with schizophrenia, regardless of study design (card version, single-trial version). In contrast, emotional modulation of attention in healthy participants seems to be influenced more strongly by study design, with decreasing influence of emotion in the card version. An alternative, more plausible explanation, is that in the card version of the Stroop-task the inability of patients with schizophrenia to narrow down attention to a word located in array of words (Boucart, Mobarek, Cuervo, & Danion, 1999) causes an increase of RT. And this effect is present for cards with incongruent colour stimuli as well as for cards with negative emotional stimuli.

Williams et al. (1996) reviewed a manifold of studies that examined the emotional Stroop-task in clinical samples, mostly patients with anxiety or depressive disorder. They concluded that the magnitude of personal concern of words to the individual is the most relevant cause of interference. Similar effects have been reported in deluded patients (Bentall & Kaney, 1989) and in healthy controls (Wingenfeld et al., 2006). However, in these studies negative or threatening words were used. Neither in previous studies (Demily et al., 2010; Phillips et al., 2005) nor in

our study the emotional words used were examined with respect to their individual emotional relevance. This may explain the differences between results, besides the fact that the card version has been found to produce greater interference than the single-trial version (Henik & Salo, 2004; Westerhausen et al., 2011). However, all studies reported an interference effect for negative words, suggesting a different impact on processing of negative and positive emotional words.

Several studies reported a speed-accuracy trade-off effect in the incongruent condition of the standard Stroop-task in patients with schizophrenia (Barch et al., 2004; Barch, Carter, Perlstein, et al., 1999; Henik et al., 2002), an effect we did not observe. In contrast, we found a significantly increased number of errors in the positive condition of the emotional Stroop-task, which could explain why the patients in our sample did not show the interference effect for positive words reported by Demily et al. (2010). However, the interference effect was observed in both healthy controls and patients, so probably the differences can better be accounted for by the different words used in their and our study for positive valence.

Neuroimaging studies have shown that a large number of brain regions such as the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate gyrus, parietal, temporal and occipital lobe, are involved in the performance of the standard and emotional Stroop-task (Compton et al., 2003; Whalen et al., 1998). As Compton et al. (2003) report, the DLPFC shows the greatest changes in BOLD-signal in the contrast between negative and high-arousal words compared to neutral words, but also for incongruent-colour words. Whalen et al. (1998) found a higher BOLD-signal in the anterior cingulate gyrus comparing the first blocks of negative and neutral stimuli within an emotional counting Stroop-task. Both studies (Compton et al., 2003; Whalen et al., 1998) used a blocked design and found a habituation of BOLD-signal differences during the task. In addition they did not find an interference effect of negative compared to neutral trials. With respect to our singe-trial design, these results can only be applied partially. However, studies in patients with schizophrenia have shown that when patients perform at the same level of accuracy as healthy controls in a standard Stroop-task patients recruit additional resources in the prefrontal lobe (I. H. Park et al., 2008). In addition, impaired performance is associated with reduced BOLD-signal in the prefrontal cortex (Weiss et al., 2003; Weiss et al., 2007). The latter results have to be viewed with some caution, firstly because an adapted Stroop-task was used, and secondly because not reaction time but accuracy was the dependent measure in this study. However, transferring these observations to our results and the fact that patients showed the same effect on interference and facilitation with longer reaction times could be explained by recruitment of additional prefrontal resources. The increase of mean RT is then the consequence of the typically observed reduced speed of processing (Gonzalez-Blanch et al., 2010).

There are some limitations in our study. First, our samples were not matched with respect to level of education. However, in spite of

significant differences between patients with schizophrenia and healthy controls, Stroop-effects did not differ between groups, so we would like to suggest that differences in time of education are not relevant for the interpretation of our data. Second, participants did not evaluate emotional words for their emotional impact (valence and arousal). Thus, we cannot exclude the possibility, that positive words did differ significantly less in their emotional impact from neutral words than the negative ones, which would explain why we could not replicate the findings of Demily et al. (2010). However, the increased error rate for positive words in the group of patients makes this assumption less probable. Finally, the group of patients was heterogeneous with respect to antipsychotic medication, and the group of untreated patients was too small to perform a separate analysis. So, we could not examine possible medication effects, but our finding that the emotional modulation of attention does not differ between patients and healthy controls reduces the relevance of this limitation.

In conclusion we found a general slowing in RT in patients with recent-onset schizophrenia during an emotional Stroop-task, but interference and facilitation effects did not differ as compared to healthy controls, neither in the cognitive, nor in the emotional Stroop-task. We suggest that these results demonstrate a general reduction in speed of processing, but that selective attention in patients with recent-onset schizophrenia is influenced by incongruence of colour words and emotional content of words in the same way as it is in healthy controls.

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Chapter 5

Emotional memory modulation in schizophrenia: an overview

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Abstract

Objective: In healthy controls (HC), the emotional charge of stimuli influences how well stimuli are remembered. Although patients with schizophrenia (SCZ) have deficits in memory and in emotional processing, studies on emotional memory modulation (EMM) in SCZ report contradictory results. The aim of this review was to investigate whether methodological differences could explain these contradictory results.

Method: We reviewed the literature to investigate if task differences could explain these differences. Due to the methodological differences, a meta-analysis was not possible.

Results: 14 studies were identified that used a total of 22 tasks tot study EMM in SCZ. Two-thirds of the tasks showed no differences in EMM between SCZ and HC. Differences in emotional memory modulation were found more often when long-term compared to short-term memory was measured, when memory instructions were implicit instead of explicit and when stronger emotional stimuli were used. An overall memory deficit or the mode-of-retrieval were not related to emotional memory modulation.

Conclusion: Deficits in emotional memory modulation in long compared to short-term memory point toward impaired emotional modulation of memory consolidation. Reduced emotional memory modulation on implicit but not explicit tasks suggests a deficit in unconsciously using emotional content to modulate memory.

Introduction

Emotional disturbances and memory deterioration were recognized as essential parts of schizophrenia (1899), even before the term schizophrenia was introduced over a hundred years ago (1916). More recent meta-analysis confirmed that overall memory impairment (e.g. Aleman, Hijman, de Haan, & Kahn, 1999; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009) and emotional disturbances (C. G. Kohler, Walker, Martin, Healey, & Moberg, 2010; Marwick & Hall, 2008) are core features of schizophrenia. An important interaction between emotion and memory in healthy controls is emotional modulation of memory, which entails that for "emotionally charged stimuli" memory is better than for "emotionally neutral stimuli"(E. A. Kensinger, 2004). Both memory deficits and emotional disturbances are widely studied in patients with schizophrenia and several studies have directly investigated emotional modulation of memory in patients with schizophrenia. Although these studies provide clues that emotional memory modulation is disturbed in patients with schizophrenia, their results are inconsistent and sometimes contradict, as Herbener pointed out in her 2008 review (Herbener, 2008). Since these studies differ in their methodology, this could explain some of the variability in the results. The aim of the current paper is to investigate how differences in methodology influence the result of studies on emotional memory modulation in patients with schizophrenia.

This paper focuses on both short-term memory (STM) and long-term memory (LTM) and its sub-processes of encoding, consolidation, storage and retrieval of stimuli (Kandel & Schwartz, 2000). The interaction between emotion and working memory has been discussed by others (for example Becerril & Barch, 2011; Linden et al., 2010). Before discussing the studies on emotional memory modulation in patients with schizophrenia, we will briefly summarize: research on memory impairment in patients with schizophrenia, on emotional processing in patients with schizophrenia, on emotional memory modulation in healthy controls and research that investigated the correlation between emotion and memory in patients with schizophrenia.

Background

Memory deficits in patients with schizophrenia

Patients with schizophrenia have a significant overall memory impairment compared to healthy controls (e.g. Aleman et al., 1999; Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Mesholam-Gately et al., 2009). There is accumulating evidence that this overall memory impairment is one of the core symptoms of schizophrenia. It is present in the early course of the disease (e.g. Albus et al., 2006; Townsend & Norman, 2004), before the start of medication (Hill, Beers, Kmiec, Keshavan, & Sweeney, 2004) and remains stable during the course of the disease (Tyson, Laws, Roberts, & Mortimer, 2005). Impaired memory performance in unaffected twins (Toulopoulou et al., 2007) and even in unaffected

relatives (see Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Snitz, Macdonald, & Carter, 2006 for meta-analysis) suggests a genetic basis. Although overall memory performance is influenced by disturbances on other cognitive domains such as speed of processing and organization, this can only in part account for the differences between patients with schizophrenia and healthy controls in memory performance (Dickinson, Ragland, Gold, & Gur, 2008; Holthausen et al., 2003), making impaired memory a primary deficit in schizophrenia.

Three observations have led to the idea that in patients with schizophrenia the self-initiation of encoding strategies is defective, but not the execution of encoding strategies (J. M. Danion, Huron, Vidailhet, & Berna, 2007): 1) patients with schizophrenia have difficulty to organize to-be-remembered stimuli spontaneously; 2) if stimuli are presented in a semantically organized way, this does not lead to a spontaneous improvement in performance in patients with schizophrenia as it does in healthy controls, and 3) memory does improve when patients with schizophrenia are told to semantically organize to be remembered stimuli. Memory impairments are related to functional outcome (Fujii & Wylie, 2003; Hofer et al., 2005) and quality of life (Fiszdon, Choi, Goulet, & Bell, 2008; Sota & Heinrichs, 2004). Although disturbances in memory are nearly unaffected by psychiatric medication (Albus et al., 2006; Hill, Schuepbach, Herbener, Keshavan, & Sweeney, 2004), they could be a target for cognitive remediation approaches (Demily & Franck, 2008; Prouteau et al., 2005) or novel drug treatments (Green, 2007). Within the literature on memory impairment in schizophrenia, there is some debate over which domains of memory (verbal vs. non-verbal, recall vs. recognition, LTM vs. STM) are more specifically affected (J. M. Danion et al., 2007; Ranganath, Minzenberg, & Ragland, 2008) and the methodological strategies best used to test these differences (Leavitt & Goldberg, 2009).

Emotional deficits in schizophrenia

Similar to disturbances in memory function, deficits in emotional domains are a core feature of schizophrenia and include the expression, experience and recognition of emotions(Trémeau, 2006). These deficits are already present in first-episode schizophrenia patients (Edwards, Pattison, Jackson, & Wales, 2001; Herbener, Hill, Marvin, & Sweeney, 2005) and are related to the severity of psychopathology (Kee et al., 2009; Christian G. Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000). Emotional disturbances also influence psychosocial functioning and quality of life (Kee, Green, Mintz, & Brekke, 2003; C. G. Kohler & Martin, 2006) and are only minimally influenced by antipsychotic medication (Herbener et al., 2005).

An often replicated finding concerns the processing of emotional stimuli (Trémeau, 2006). Patients with schizophrenia are impaired in using facial cues for social judgment (Marwick & Hall, 2008) and have a decreased emotional experience (Aleman & Kahn, 2005). These disturbances are often accompanied by reduced facial expressions in patients with schizophrenia themselves. Functional neuroimaging studies have

demonstrated that these impairments are associated with a reduced BOLD-signal change in the amygdala (Gur et al., 2002). Patients with schizophrenia nevertheless produce the same physiological responses (breathing rate, skin conductance response and systolic blood pressure) as healthy controls when exposed to emotional stimuli (Hempel, Tulen, van Beveren, Mulder, & Hengeveld, 2007). When rating emotional stimuli, patients with schizophrenia report diminished valence ratings in some studies (Cohen & Minor, 2010), while other studies report no differences (Bigelow et al., 2006; Burbridge & Barch, 2007). These contradictory results might in part be due to the different ways emotional experience is measured; differences are usually larger when hedonic and aversive feelings are sampled independently compared to when they are regarded as the extremes of a single continuum.

Emotional memory modulation in healthy controls

In healthy controls memory is facilitated by emotional compared to neutral stimuli (e.g. E. A. Kensinger & Corkin, 2003a, 2003b; LaBar & Cabeza, 2006) when using words, pictures or faces as stimuli. This is sometimes called emotional memory enhancement. Because in patients with schizophrenia it is less clear whether emotion enhances or decreases memory, in this review we will talk about Emotional Memory Modulation (EMM). Possible explanations for EMM in healthy controls include: increased attention during encoding for emotional compared to neutral stimuli, increased engagement of higher cognitive functions during encoding and recall for emotional stimuli, mood congruency effects, salience effects (Herbener, 2008) and enhanced consolidation (S. Hamann, 2001; McGaugh, 2000). This advantage comes at the cost of an impeding effect for surrounding stimuli (Strange, Hurlemann, & Dolan, 2003) and there is also evidence that emotion can create a response bias in memory tasks (Maratos, Allan, & Rugg, 2000; Sergerie, Lepage, & Armony, 2007). Although there is some evidence that EMM in healthy controls is more pronounced in LTM than STM (Quevedo et al., 2003), others found the same degree of EMM in LTM and STM (Brierley, Medford, Shaw, & David, 2007). Furthermore, differences between EMM for STM and LTM are hard to compare within the same study because an immediate retrieval task can interfere with the enhanced consolidation of emotional material in LTM (Wolf, 2012).

Conform the model proposed by Cahill and McGaugh (1996), studies using neuroimaging techniques have repeatedly shown that EMM occurs under influence of the amygdala (S. B. Hamann, Ely, Grafton, & Kilts, 1999), especially for negative stimuli (Erk et al., 2003). The amygdala is involved in encoding, consolidation and retrieval in memory for both negative and positive stimuli (Adolphs, Denburg, & Tranel, 2001; Dolan, Lane, Chua, & Fletcher, 2000; S. Hamann, 2001). The amygdala acts in concert with both the prefrontal cortex (Dolcos, LaBar, & Cabeza, 2004) and the hippocampus (Phelps, 2004) in emotional memory and impaired communication between these three systems is hypothesized to

underlie affective flattening and emotion recognition deficits in patients with schizophrenia (Aleman & Kahn, 2005). Emotional stimuli can exert influence on long term memory by increasing activity in the amygdala, which than increases long term potentiation in the hippocampus (Abe, 2001). This process is mediated by dopamine (Gibbs, Naudts, Spencer, & David, 2007; Herbener, 2008), the neurotransmitter that has been consistently linked to the pathogenesis of schizophrenia (Os van & Kapur, 2009).

Studies on the correlation between emotion and memory in schizophrenia

Several studies report correlations between emotional deficits and overall memory performance in patients with schizophrenia, but results are contradictory. While Pijnenborg and colleagues (2007) show that recognition of emotional prosody is moderately correlated with verbal memory ($p < .05$), Kee and colleagues (1998) found no significant correlation between immediate memory and emotion perception in patients with schizophrenia.

Affective flattening has been associated with decreased performance for verbal memory (Gur et al., 2006) and non-verbal memory (Berenbaum, Kerns, Vernon, & Gomez, 2008). Lysaker and colleagues (2000) reported that especially scores on PANSS (Kay, Fiszbein, & Opler, 1987) items regarding emotional discomfort were strongly associated with memory performance.

In a recent study by Satterthwaite and colleagues (Satterthwaite et al., 2010) participants performed an emotional face recognition task during fMRI. In the encoding phase faces displayed threat (fear, anger) or nonthreat (sadness, happiness) expressions, whereas in the recognition phase the faces had neutral expressions. They found that patients with schizophrenia performed the task slower but equally accurate as healthy controls. This was coupled with reduced activation of frontoparietal regions involved in recognition memory and increased activity in limbic regions in patients with schizophrenia. So it appears that by employing alternative or compensatory neuronal strategies patients with schizophrenia can achieve similar performance levels as healthy controls.

It is clear that patients with schizophrenia have both an overall memory deficit and suffer from emotional disturbances. Both Herbener and colleagues (2008) and Becerril and Barch (2011) suggested that in patients with schizophrenia deficits in emotional functioning involve the effective integration of emotion and cognition. This would mean that emotional memory modulation in patients with schizophrenia should also be disturbed. Yet the literature on EMM in patients with schizophrenia is divided, i.e. some studies show intact EMM in patients with schizophrenia while others report disturbances (Herbener, 2008). Because the studies differ in methodology this could explain some of the variability in the results, similar to the variability caused by methodological differences observed by Leavitt and Goldberg (Leavitt & Goldberg, 2009) in the literature on episodic memory in schizophrenia.

Aims of the study

The aim of this paper is to investigate how differences in methodology influence the results of studies on EMM in patients with schizophrenia and subsequently to consider what we can learn about EMM in patients with schizophrenia when we account for these differences.

Methods

We performed a literature search using PubMed, Web-of-Science and Google Scholar with the search strings "schizophrenia AND emotio* AND memory" and "schizophrenia AND affect* AND memory" to identify potentially relevant articles (last search: December 2011). We manually searched the reference lists of selected articles for other relevant articles.

To be included in the current review, studies had to: 1) be in English, 2) compare performance of patients with schizophrenia to healthy controls and 3) compare memory for emotional stimuli to either neutral stimuli within the same task or compare memory for negative and positive stimuli within the same task.

Studies were excluded if they: primarily investigated working memory; primarily investigated emotion recognition or learning: were reviews; or sampled emotional experience and memory separately. Inherent to comparing studies using different methods, a meta-analysis was not possible and therefore we could only compare data qualitatively and not quantatively.

Results

Our search resulted in 14 studies (Calev & Edelist, 1993; J.-M. Danion, Kazes, Huron, & Karchouni, 2003; Hall, Harris, McKirdy, Johnstone, & Lawrie, 2007; Harvey, Bodnar, Sergerie, Armony, & Lepage, 2009; Herbener, Rosen, Khine, & Sweeney, 2007; Kline, Smith, & Ellis, 1992; Koh, Grinker, Marusarz, & Forman, 1981; Koh, Kayton, & Peterson, 1976; Lakis et al., 2011; Mathews & Barch, 2004; Neumann, Blairy, Lecompte, & Philippot, 2007; Neumann, Philippot, & Danion, 2007; Sergerie, Armony, Menear, Sutton, & Lepage, 2010; Whalley et al., 2009) (which will be indicated by Roman numerals in the rest of this paper) that are summarized in table 1. For the studies that used multiple tasks to investigate emotional memory modulation, each task (indicated by a lower case letter in table 1) is evaluated separately (22 tasks in total) since the aim of this paper is to focus on methodological differences. The studies had relatively small sample sizes; average sample size for patients with schizophrenia 23.0, maximum 37 and average sample size for healthy controls 21.9, maximum 37.

Emotional memory modulation in healthy controls

The performance of healthy controls gives an indication of the comparability of these tasks to the literature on EMM in healthy controls. In healthy controls, memory for negative stimuli usually is better compared to memory for neutral stimuli (Elizabeth A. Kensinger, 2009).

However, out of the 13 tasks on negative compared to neutral stimuli only 7 reported memory enhancement for negative stimuli (tasks IVb, V, VIa, VII, VIIIa,b,c), while 4 (tasks III, IVa, XIII and XIV) reported no modulation en 2 (VIb and XI) even reported impaired memory for negative stimuli.

There is some evidence that positive stimuli enhance memory in healthy controls (Elizabeth A. Kensinger, 2009). We found 14 tasks comparing memory for positive to neutral stimuli. In 11 tasks (IVb, V, VIa, VII, VIIIa,b,c, XI, XII, XIII and XIV) memory in healthy controls was enhanced for positive compared to neutral stimuli, in 2 tasks (II and IVb) there was no memory modulation for positive stimuli and in 1 task (VIb) memory was even reduced for positive stimuli. For both positive and negative stimuli, a lack of memory enhancement was found only in STM and never in LTM tasks.

17 tasks compared memory for negative to positive stimuli. In 9 tasks (Ia,c, IIa,b,c, VII, XI, XIII and XIV) memory for positive stimuli was better than for negative stimuli, 3 (VIb, IX and X) showed the opposite pattern and in 5 (Ib, IVa,b, V and VIa) no difference was found, which is similar to the mixed results reported in the literature (LaBar & Cabeza, 2006; Sergerie et al., 2007).

Consequently, some caution has to be taken in relating these results to the literature of EMM in healthy controls, especially for negative stimuli. A possible cause for the different result for negative compared to neutral stimuli could be that the tasks used to compare EMM in patients with schizophrenia to healthy controls were less demanding than the tasks used to study EMM in healthy controls alone.

Emotional memory modulation in schizophrenia

Of the 22 tasks in table 1, 8 found differences in EMM between patients with schizophrenia and healthy controls. In 3 tasks (Ia, IIb,c) patients with schizophrenia had no memory enhancement for positive compared to negative stimuli although healthy controls did. In 2 tasks (IVb and VII) patients with schizophrenia missed the memory enhancement for positive compared to neutral stimuli which was found in healthy controls and in 1 task (VIIIc) memory enhancement for all emotional stimuli was reduced in patients with schizophrenia compared to healthy controls. 1 task (IX) reported that in patients with schizophrenia memory for positive stimuli was enhanced compared to negative stimuli while in healthy controls the pattern was reversed; better memory for negative compared to positive stimuli. In the last task (XIV) memory in healthy controls was enhanced for (high arousal) positive stimuli while in patients with schizophrenia it was only enhanced for (low arousal) negative stimuli. In the other 14 tasks (Ib,c, IIa, III, IVa, V, VIa,b, VIIIa,b, X, XI, XII and XIII) the presence and direction of EMM was the same in patients with schizophrenia as in healthy controls (although the presence and direction of EMM differed between tasks).

There is some evidence for reduced EMM in patients with

schizophrenia, however two-thirds of the tasks shows no difference in EMM in patients with schizophrenia. In order to explain these inconsistent results we systematically compared the tasks that did find differences in EMM with the tasks that did not find differences in EMM on several methodological factors to see if these methodological factors could explain the different outcomes.

Overall memory and emotional memory modulation

It is possible that disturbances in EMM are a non-specific consequence of reduced memory performance. To investigate this possibility, we compared the tasks with and without differences in EMM on the presence of an overall memory deficit in patients with schizophrenia. When differences in EMM were present, an overall memory deficit was present in 5 tasks (IVb, VII, VIIIc, IX, XIV), 3 tasks (Ia, IIb,c) reported no overall memory deficit.

In the 14 studies that found no difference in EMM, an overall memory deficit was present in 9 tasks (IIa, IVa, V, VIa, VIIIa,b, X, XI, XIII) while 5 tasks (Ib,c, III, VIb and XII) reported no overall memory deficit. Although disturbances in EMM are subtle, and could disappear when general disturbances in memory performance are present in patients with schizophrenia (see also Murray, Corlett, & Fletcher, 2010), these results suggest that disturbances in EMM can appear independently from an overall memory impairment.

Short-term memory versus long-term memory and emotional memory modulation

Differences between STM and LTM tasks could point toward disturbances in specific processes involved in EMM such as encoding, consolidation or retrieval. In the tasks that found differences in EMM, half of the tasks (Ia, IIb,c, and XIV) tested STM, while the other half (IVb, VII, VIIIc and IX) tested LTM. In the 14 studies that found no difference in EMM, STM was tested in 12 tasks (Ib,c, IIa, III, IVa, V, VIa,b, VIIIa, XI, XII and XIII) while 2 tasks (VIIIb, X) reported on LTM.

2 studies (IV and VIII) compared performance on an emotional STM task (IVa/VIIIa) to performance on an emotional LTM task (IVb/VIIIb). While study VIII found no difference in emotional memory modulation between patients with schizophrenia and healthy controls, study IV found normal memory enhancement for the STM task and less memory enhancement for positive compared to neutral stimuli in the LTM task in patients with schizophrenia compared to healthy controls. These findings suggest that in patients with schizophrenia disturbances in emotional memory enhancement are found more often in LTM then in STM.

Recall versus recognition and emotional memory modulation

Differences between tasks using recall and recognition could indicate specific disturbances in the underlying retrieval processes. When differences in EMM were present, recall was tested in 3 tasks (Ia, IIb,

Table 1: Studies investigate emotional memory modulation

Authors and year	Study/ task	Sample		Overall Memory	Delay	Type	Stimulus type	Memory Instructions
		SCZ	HC					
Koh, Kayton et al. 1976	Ia	18	19	SCZ=HC	none	Recall	Words	Implicit
	Ib	18	19	SCZ=HC	none	Recog	Words	Implicit
	Ic	18	19	SCZ=HC	none	Recall	Words	Explicit
Koh, Grinker et al. 1981	IIa	16	16	SCZ<HC	none	Recall	Words	Explicit
	IIb	16	16	SCZ=HC	none	Recall	Words	Implicit
	IIc	16	16	SCZ=HC	none	Recog	Faces	Implicit
Kline, Smith et al. 1992	III	27	15	SCZ=HC	none	Recog	Faces	Implicit
Calev and Edelist 1993	IVa	14	14	SCZ<HC	none	Recall	Words	Explicit
	IVb	14	14	SCZ<HC	48h	Recall	Words	Explicit
Danion, Kazes et al. 2003	V	24	24	SCZ<HC	15 min	Recog	Words	Explicit
Mathews and Barch 2004	VIa	27	28	SCZ<HC	none	Recall	Words	Implicit
	VIb	27	28	SCZ=HC	none	Recog	Words	Implicit
Herbener, Rosen et al. 2007	VII	33	28	SCZ<HC	24h	Recog	Photos	Implicit
Hall, Harris et al. 2007	VIIIa	20	20	SCZ<HC	10 min	Recall	Photos	Implicit
	VIIIb	20	20	SCZ<HC	21 days	Recall	Photos	Implicit
	VIIIc	20	20	SCZ<HC	21 days	Recog	Photos	Implicit
Neumann, Blairy et al. 2007	IX	20	20	SCZ<HC	24h	Recog	Photos	Implicit
Neumann, Philippot et al. 2007	X	24	24	SCZ<HC	24h	Recog	Photos	Implicit
Harvey, Bodnar et al. 2009	XI	27	27	SCZ<HC	none	Recog	Faces	Implicit
Whalley, McKirdy et al. 2009	XII	15	14	SCZ=HC	10 min	Recog	Photos	Explicit
Sergerie, Armony et al. 2010	XIII	20	20	SCZ<HC	none	Recog	Faces	Explicit
Lakis, Jiménes et al. 2011	XIV	37	37	SCZ<HC	15 min	Recog	Photos	Implicit

Table 1 continued: Studies investigate emotional memory modulation

Authors and year	Deficit in EMM present	Memory for POS. compared to NEU.		Memory for NEG. compared to NEU.		Memory for POS. compared to NEG.	
		SCZ	HC	SCZ	HC	SCZ	HC
Koh, Kayton et al. 1976	Yes					P=N	P>N
	No					P=N	P=N
	No					P>N	P>N
Koh, Grinker et al. 1981	No					P>N	P>N
	Yes					P=N	P>N
	Yes					P=N	P>N
Kline, Smith et al. 1992	No	↔	↔	↔	↔		
Calev and Edelist 1993	No	↔	↔	↔	↔	P=N	P=N
	Yes	↔	↑	↑	↑	P<N	P=N
Danion, Kazes et al. 2003	No	↑	↑	↑	↑	P=N	P=N
Mathews and Barch 2004	No	↑	↑	↑	↑	P=N	P=N
	No	↓	↓	↓	↓	P<N	P<N
Herbener, Rosen et al. 2007	Yes	↔	↑	↑	↑	P<N	P>N
Hall, Harris et al. 2007	No	↑	↑	↑	↑		
	No	↑	↑	↑	↑		
	Yes	↔	↑	↔	↑		
Neumann, Blairy et al. 2007	Yes					P>N	P<N
Neumann, Philippot et al. 2007	No					P<N	P<N
Harvey, Bodnar et al. 2009	No	↑	↑	↓	↓	P>N	P>N
Whalley, McKirdy et al. 2009	No	↑	↑				
Sergerie, Armony et al. 2010	No	↑	↑	↔	↔	P>N	P>N
Lakis, Jiménes et al. 2011	Yes	↔	↑*	↑**	↔	P=N	P>N

** Only for high arousal positive stimuli, not for low arousal positive stimuli,** Only for low arousal negative stimuli, not for high arousal negative stimuli*

IVb) and 5 tasks (IIc, VII, VIIIc, IX and XIV) tested recognition. In the 14 studies that found no difference in EMM, recall was tested in 6 tasks (Ic, IIa, IVa, VIa and VIIIa,b) while 8 tasks (Ib, III, V, VIb, X, XI, XII and XIII) reported on recognition.

3 studies (I, VI and VIII) compared performance for recall and recognition for the same stimuli after the same time interval. Studies I and VI tested both recall and recognition immediately after presentation of the stimuli and found no difference in emotional memory modulation between patients with schizophrenia and healthy controls. In study VIII participants were tested 21 days after stimulus presentation and in patients with schizophrenia EMM was reduced in the recognition task (VIIIc) but not in the recall task (VIIIb). In summary, emotional enhancement effects on memory appear to be independent from the mode of retrieval.

Stimulus type and emotional memory modulation

Picture of scenes, faces and words are processed in different areas of the brain. Patients with schizophrenia have shown different degrees of deficit in processing and remembering these types of stimuli and we speculated that deficits in EMM would be influenced by the type of stimulus. Differences in EMM were found in 4 task using scenes (VII, VIIIc, IX and XIV), 1 tasks using faces (IIc) and 3 tasks with words (Ia, IIb, IVb). The studies that found no difference in EMM used scenes 4 times (VIIIa,b, X, XII), faces 3 times (III, XI and XIII) and words 7 times (Ib,c, IIa, IVa, V, VIa,b). In short; in both verbal and visual memory there is equal evidence for EMM, although it is somewhat stronger for the pictures of scenes and objects then for the pictures of faces showing an emotional expression. This is in line with Horan and colleagues (Horan, Green, Kring, & Nuechterlein, 2006) who found that memory was similar for patients with schizophrenia and healthy controls for movie fragments, either neutral or emotional, as well as for food (delicious or non-delicious) although this effect might have been caused by a ceiling effect in both groups.

Implicit versus explicit memory instructions and emotional memory modulation

EMM can be used consciously or unconsciously to boost memory. Although it is difficult to measure the strategies participants use to boost their memory, differences between implicit and explicit memory tasks can point toward deficits in the ability to initiate such strategies. When differences in EMM were present, no instructions about a forthcoming memory task were given (implicit memory task) in 7 tasks (Ia, IIb,c, VII, VIIIc, IX, XIV), while differences in EMM was found in only 1 task (IVb) that gave explicit memory instructions. In the 14 studies that found no difference in EMM (Ib,c, IIa, III, IVa, V, VIa,b, VIIIa,b, X, XI, XII, XIII), 8 tasks (Ib, III, VIa,b, VIIIa,b, X and XI) used a implicit memory task, while 6 tasks (Ic, IIa, IVa, V, XII and XIII) used explicit memory instructions. So disturbances in EMM are found more often with implicit memory tasks than when explicit memory instructions are given.

Table 2: Correlations between psychopathology and emotional memory modulation

Authors and year	Study	Diag-noses	PANSS	SANS	SAPS	BPRS	Maine	Chap-man	Influence of clinical symptoms on emotional memory enhancement in SCZ
Kline, Smith et al. 1992	III	RDC				•	•		There was no association between clinical symptoms and recognition of POS and NEG faces although non-paranoid SCZ were deficient in overall labeling of facial affect compared to paranoid SCZ and non-paranoid SCZ had a recognition deficit for geometrical figures compared to paranoid SCZ.
Mathews and Barch 2004	VI	SCID	•						Blunted affect was associated with less emotional memory enhancement for POS and NEG stimuli in both recall and recognition. Hallucinations, de-pression, conceptual disorganization and delusions had no correlation with emotional memory enhancement.
Herbener, Rosen et al. 2007	VII	SCID	•					•1	Recognition accuracy was not correlated with PANSS scores or anhedonia scores. Anhedonia scores were inversely correlated with valence and arou-sal ratings for positive stimuli in HC but not in SCZ.
Hall, Harris et al. 2007	VIII	CC	•						PANSS negative symptoms scores were correlated with recall of NEU scenes and recognition of both NEU and NEG scenes. PANSS negative symptoms scores were not correlated witch memory for POS scenes. PANSS positive and general symptoms scores were not correlated with emotional memory enhancement.
Neumann, Blairy et al. 2007	IX	CC		•	•	•			Na correlation was found between memory of emotional memory enhance-ment and BPRS, SANS and SAPS scores and sub-scores.
Neumann, Philippot et al. 2007	X	CC		•	•	•			Na correlation was found between memory of emotional memory enhance-ment and BPRS, SANS and SAPS scores and sub-scores.
Harvey, Bodnar et al. 2009	XI	SCID		•	•			•2	There was no correlation between emotional memory enhancement and social anhedonia.
Lakis, Jimé-nes et al. 2011	XIV	SCID	•						Correlations between EMM and PANSS scores were not analyzed

RDC: Research Diagnostic Criteria
SCID: Structured Clinical Interview for DSM-IV
CC: Clinical Consensus
NEU: neutral
POS: positive
NEG: negative

PANSS: Positive And Negative Symptom Scale
SANS: Scale for the Assessment of Negative Symptoms
SAPS: Scale for the Assessment of Positive Symptoms
BPRS: Brief Psychiatric Rating Scale
Maine: Maine Scale of Paranoid and Nonparanoid Schizophrenia
Chapman: 1 Chapman Social and Physical Anhedonia Scales/ 2 Chapman Revised Social Anhedonia Scale

Valence and arousal and emotional memory modulation

For 9 tasks (VIa,b, VII, VIIIa,b,c, XI, XII and XIV) valence and arousal ratings were provided. From these, only 2 (VII and VIIIc) found differences in EMM between healthy controls and patients with schizophrenia. They show a trend for EMM to increase when valence ratings are more negative or more positive and this trend seems to be even stronger in patients with schizophrenia than in healthy controls. The results for arousal are harder to interpret because most studies only used medium to high arousal and no low arousal stimuli. Lankis et al. (study XIV, 2011) looked specifically into the effect of arousal by using fMRI and found that at both the behavioural and neurofunctional level, patients with schizophrenia closely resemble healthy controls.

Psychopathology and emotional memory modulation

7 studies (III, VI, VII, VIII, IX, X and XI) reported data on correlations between psychopathology and emotional memory modulation (see table 2). Although 2 studies (VI and VIII) reported that EMM was correlated with negative symptoms, the other 5 (III, VII, IX, X and XI) reported no correlation. None of the studies reported a correlation between EMM and positive symptoms.

Discussion

Our review of the literature shows that the data on emotional memory modulation in patients with schizophrenia are contradictory. Two-thirds of the tasks showed no differences in EMM between patients with schizophrenia and healthy controls. The tasks that did report a difference showed inconsistent results; either deficits in EMM for positive stimuli, negative stimuli or both kinds of stimuli. We reviewed the methodological differences between tasks and found that disturbances in EMM are reported more often in tasks where: (1) long-term instead of short-term memory was measured, (2) memory instructions were implicit instead of explicit, and (3) stronger emotional stimuli were used. Neither overall memory deficit nor mode-of-retrieval were related to differences in emotional memory modulation. The literature shows no evidence that these differences are related to positive symptoms and only 2 studies report a relation between negative symptoms and EMM while 5 show no relation.

There are several ways tasks differences could influence emotional memory modulation. First of all, because patients with schizophrenia report the same valence ratings as healthy controls while their performance on emotional memory tasks is decreased, this agrees with the theory that deficits in emotional functioning involve the effective integration of emotion and cognition (Becerril & Barch, 2011; Herbener et al., 2008). Since emotional memory modulation is more disturbed in long-term compared to short-term memory, EMM appears to be disturbed not at the level of encoding but probably further downstream at the levels of consolidation, storage and retrieval. Previous reports have demonstrated sleep dependent disturbances in memory consolidation in patients with schizophrenia

(see Manoach & Stickgold, 2009 for review). In healthy controls consolidation after sleep is better for emotional than neutral stimuli (Payne & Kensinger, 2010). Consolidation is modulated by the amygdala (Cahill et al., 1996; McGaugh, 2000), a structure repeatedly linked to (emotional) dysfunctions in patients with schizophrenia (Aleman & Kahn, 2005; Phillips, Drevets, Rauch, & Lane, 2003). It is possible that in patients with schizophrenia the emotional modulation of the consolidation process via the amygdala is disturbed. Patients with schizophrenia show comparable emotional memory modulation to healthy controls in short-term memory tasks, indicating that the emotional memory modulation processes that are active at encoding remain intact, although these processes are also, at least in part, mediated by the amygdala (S. Hamann, 2001). The amygdala alone is not enough to facilitate emotional memory modulation (Anderson, Yamaguchi, Grabski, & Lacka, 2006), it works in concert with other parts of the medial temporal lobe such as the hippocampus to facilitate emotional memory modulation, brain structures where altered activation is found in patients with schizophrenia during memory tasks (Dere, Pause, & Pietrowsky, 2010; Whalley et al., 2009).

A second possibility is that since disturbances in emotional memory modulation are mainly found in tasks without explicit memory instructions, patients with schizophrenia have difficulty automatically or unconsciously using emotional content to enhance memory (see also Ranganath et al., 2008). This is in line with the theory by Danion and colleagues that in patients with schizophrenia the self-initiation of encoding strategies is defective, but not the execution of encoding strategies (J. M. Danion et al., 2007). Patients with schizophrenia could achieve normal performance levels by employing alternative or compensatory neural strategies compared to healthy controls (see also Lakis et al., 2011). EMM can be seen as one compensatory strategy that is used when an overall memory deficit is present. This could explain why disturbances in emotional memory modulation are already seen when there is no difference in overall task performance. Or alternatively, subtle disturbances in EMM could be obscured by a large overall memory deficit in the more demanding tasks. In one study (Sergerie et al., 2010) patients with schizophrenia had an overall lower memory accuracy while emotional memory modulation was comparable to healthy controls. The investigators found emotion-specific differences in brain activation between patients with schizophrenia and healthy controls, which is in line with the theory by Murray et al. (Murray et al., 2010) that in patients with schizophrenia performance can be relative intact in the presence of abnormal brain function. It is also possible that patients with schizophrenia use different cognitive EMM strategies compared to healthy controls, which could give patients with schizophrenia the same EMM on performance level as healthy controls (Sergerie et al., 2010).

A third possibility would be that in patients with schizophrenia identification of facial emotions is intact while a deficit in judging emotional intensity is present (Pomarol-Clotet et al., 2009). This could mean that (at least for the tasks that used emotional faces) emotional memory

modulation depends more on the intensity than the type of emotion. This puts patients with schizophrenia on a disadvantage, since they require greater emotional signal strength to process emotional faces (Norton, McBain, Holt, Ongur, & Chen, 2009). The mixed results obtained in tasks using faces could also be influenced by patients with schizophrenia needing more facial information to recognize the emotional expression of faces (Lee, Gosselin, Wynn, & Green, 2010) which means that the stimuli are relatively more complex for patients with schizophrenia compared to healthy controls.

Fourthly, if emotional memory modulation was reduced at the level of retrieval, one would expect that a task using recall would be affected more compared to a relatively easier recognition tasks. All picture tasks that reported differences were recognition tasks while all word tasks reporting differences were recall tasks, which is inherent to the fact that retrieval of pictures is usually tested with recognition and retrieval of words with recall. In their review on recognition memory Pelletier et al. found that memory impairment in patients with schizophrenia was increased for nonverbal compared to verbal stimuli (Pelletier, Achim, Montoya, Lal, & Lepage, 2005). In our review there is equal evidence for disturbances in emotional memory modulation in words and photographs, although it is stronger for the pictures of scenes and objects then for the pictures of faces showing an emotional expression.

Finally, in the past memory deficits and emotional disturbances have been correlated with both negative and positive symptoms in patients with schizophrenia. Our literature search only found moderate evidence that emotional memory modulation is related to negative symptoms. This could mean that deficits in emotional memory modulation are a core deficit in patients with schizophrenia and can be present independent from positive or negative symptoms. It could also be caused by the fact that patients with schizophrenia who have severe positive or negative symptoms are not able to participate is some of the demanding tasks that are used to measure emotional memory modulation. Since only a few studies provided specific data on positive or negative symptoms, this question can not be answered at this time.

Meta-analysis of the results was not possible since the different studies reviewed in this paper not only used different methodologies, but also used different ways to present and analyze the results (hit-rates, corrected hit rates, response bias, etc). This made it also impossible to correct for age at onset and gender, despite the fact that these factors can influence memory impairments in schizophrenia (van der Werf et al., 2012). Another limitation was that some of the studies were performed before the introduction of our current diagnostic criteria for schizophrenia in the DSM-III (American Psychiatric Association Task Force on Nomenclature and Statistics, 1980) which makes generalization more difficult. Because emotional memory modulation is influenced by dopamine levels in the brain (Gibbs et al., 2007; Subramanian, Hindle, Jackson, & Linden, 2010), it is possible that antipsychotic medications reduce emotional

memory modulation. Furthermore, drugs with GABAergic or anticholinergic action have been show to influence EMM in healthy controls (Kamboj & Curran, 2006). Unfortunately, there was insufficient data to correct for medication effects. On the other hand, although the patients with schizophrenia in all the studies used antipsychotic medications, reduced emotional memory modulation was only found in a third of these studies, which means that antipsychotic medication alone cannot account for all the differences in emotional memory modulation in patients with schizophrenia compared to healthy controls.

When reviewing the literature on emotional memory modulation in patients with schizophrenia it is clear that the results are conflicting, with only a third of the tasks reporting deficits in EMM in patients with schizophrenia. Although this may in part be a consequence of the use of small sample sizes, we also found indications that the heterogeneity in the results is caused by several methodological factors. Emotional memory modulation is more reduced in patients with schizophrenia in long-term memory than in short-term memory. This could be a consequence of defective emotional memory modulation through the amygdala in the consolidation phase of long-term memory. Comparison of implicit and explicit memory tasks suggests that patients with schizophrenia can use emotional content as a strategy to enhance memory but have difficulty automatically or unconsciously initiating this strategy. An overall memory deficit and the mode of retrieval of stimuli did not influence emotional memory modulation and there is only moderate evidence that emotional memory modulation is related to negative symptoms.

Failing to integrate emotional experience in memory consolidation could contribute to anhedonia in patients with schizophrenia (Herbener et al., 2007). A further understanding of the disturbances in emotional memory modulation could not only bring us a further understanding of some of the core features of schizophrenia but also an opportunity to influence memory performance and with that the quality of life in patients with schizophrenia. In light of the results of our review of the literature, it would be of special interest to investigate either consolidation (by comparing LTM to STM), or using emotion as an enhancement strategy (by comparing explicit to implicit memory instructions) within one study where stimuli are rated for valence and arousal.

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Chapter 6

Preserved emotional memory modulation in recent onset schizophrenia

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under review

Abstract

Patients with schizophrenia have severe memory impairments and emotional deficits. Studies investigating emotional memory modulation (EMM) in schizophrenia however show contradictory results, possibly due to methodological differences and small group size. We investigated whether impaired EMM is already present in Recent Onset Schizophrenia patients (ROS) and whether impairments in EMM are task or stimulus dependent. 45 ROS en 37 Healthy Control (HC) male participants matched for age performed visual and verbal short-term (immediate recall) and long-term (after 24h recognition) memory tasks with neutral, negative and positive stimuli. On all tasks overall memory performance for ROS was significantly below that of HC. Although EMM varied by task and type of stimulus, none of the tasks showed a difference in EMM between ROS and HC. There were no differences between ROS and HC in the way emotion modulates different memory domains. This could mean that EMM is spared in the early course of schizophrenia.

Abbreviations

ROS	Recent Onset Schizophrenia
HC	Healthy controls
STM	Short Term Memory
LTM	Long Term Memory
EMM	Emotional Memory Modulation

Introduction

Memory deterioration and emotional disturbances have been recognized as core features of schizophrenia since the early descriptions of the disease (Bleuler, 1916). More recent meta-analyses confirmed these impairments in both overall memory (Aleman, Hijman, de Haan, & Kahn, 1999; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009) and emotional domains (Marwick & Hall, 2008) in patients with schizophrenia. In Healthy Controls (HC) memory is facilitated by emotional compared to neutral stimuli when using words, pictures or faces as stimuli (Kensinger & Corkin, 2003; Kohler, Walker, Martin, Healey, & Moberg, 2010; LaBar & Cabeza, 2006). It has been suggested that in schizophrenia there are disturbances in the effective integration of emotion and cognition (Becerril & Barch, 2011; Herbener, Song, Khine, & Sweeney, 2008). Anticevic and Corlett (2012) argue that cognitive and emotional impairments not only interact, but that they share important pathophysiological features at the neural level, such that disruptions caused by schizophrenia can affect both processes and the interaction between these processes (Anticevic & Corlett, 2012).

Several studies have investigated emotional memory modulation (EMM) in patients with schizophrenia. Although two thirds of studies investigating EMM found no differences in EMM between patients with schizophrenia and HC, the remaining studies provide clues that EMM in schizophrenia is affected differently in short (STM) and long-term memory (LTM) (chapter 5). In patients with schizophrenia disturbances in EMM are found three times more often in tasks investigating LTM (Calev & Edelist, 1993; Hall, Harris, McKirdy, Johnstone, & Lawrie, 2007; Herbener, Rosen, Khine, & Sweeney, 2007) than in tasks examining STM (Koh, Grinker, Marusarz, & Forman, 1981; Koh, Kayton, & Peterson, 1976; Lakis et al., 2011; Neumann, Blairy, Lecompte, & Philippot, 2007). Since the main difference between short and long-term memory tasks is consolidation, it has been suggested that an important problem with EMM in schizophrenia lies at the level of consolidation, similar to the disturbances in non-emotional memory found in schizophrenia (Manoach & Stickgold, 2009).

Studies investigating EMM in patient groups mostly consisted of chronic patients of both genders although evidence suggests that in schizophrenia age at onset and gender (van der Werf, Kohler, Verkaaik, Verhey, & van Os, 2012) influence memory impairments. There is some evidence that memory impairments are related to psychopathology (Lysaker, Bell, Greig, & Bryson, 2000), but numerous studies found no relation between disturbances in EMM and psychopathology of patients (chapter 5). Impairments in EMM in both the visual (Hall et al., 2007; Herbener et al., 2007; Lakis et al., 2011; Neumann et al., 2007) and verbal (Calev & Edelist, 1993; Koh et al., 1981; Koh et al., 1976) domain are reported, however there are no studies comparing these two types of stimuli for both STM and LTM within the same sample.

The aim of our study was to investigate three different aspects of EMM in patients with schizophrenia, 1) whether impairments in EMM are present in recent onset schizophrenia patients (ROS), 2) are possible impairments differently present in long or short term memory, 3) are possible impairments differently present in the verbal or visual domain. To answer these questions, we tested long and short-term visual and verbal memory in a group of male ROS and compared their performance to age and gender matched HC.

Methods

Participants

Forty-nine male patients were recruited at the Department of Psychiatry of the Erasmus Medical Center in Rotterdam, the Netherlands. All patients met criteria for schizophrenia (either at time of testing or after 6 months of follow-up). Diagnoses were based on clinical consensus and confirmed using the Structured Clinical Interview for DSM-IV Axis I (SCID-I) (First, 2002). Inclusion criteria were normal or corrected vision and age between 18 and 35; mean age in years was 23.6 (S.D. 4.3 years). Because we only wanted to include recent-onset schizophrenia patients, we excluded patients with illness duration of more than 5 years counting from the occurrence of either positive symptoms or clear limitations in social or occupational functioning. This method yields a relatively long duration of illness when compared with assessing only positive symptoms. Mean duration of illness was 14.8 months (S.D. 16.9 months). Thirty-seven out of 49 ROS were using anti-psychotic drugs at the time of testing (see also table 1).

Other exclusion criteria for patients were: any co-morbid psychiatric or neurologic disorder including substance related disorders, use of more than one anti-psychotic drug and IQ below 75. To asses current psychopathology, we used the Positive and Negative Syndrome Scale (PANSS, Kay, Fiszbein, & Opler, 1987) as a general psychopathology indicator. We used the Scale for the Assessment of Negative Symptoms (SANS, Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS, Andreasen, 1984) to measure current negative and positive psychopathology more specifically (see table 1 for psychopathology ratings). The Dutch 20-item version Subjective Well-being under Neuroleptics scale (SWN, Haan de, Weisfelt, Dingemans, Linszen, & Wouters, 2002) was used to evaluate well-being. The Dutch Adult Reading Test (DART) (Schmand, Bakker, Saan, & Louman, 1991) was used to estimate premorbid verbal intelligence and the Raven Progressive Matrices (Raven, 2006) was used for non-verbal intelligence.

Male Healthy Controls (HC) were recruited through advertisements on internet and word-of-mouth referrals. Mean age was 23.1 years (S.D. 4.3 years). Additional exclusion criteria for HC were; presence of any psychiatric disorder or presence of a first or second generation family member with a past or present psychotic disorder.

This study was part of a larger project investigating the interaction between emotion and cognition in ROS, which included several cognitive tasks, assessments and interviews over two consecutive days. All participants gave informed consent and the study was conducted in compliance with the Helsinki Declaration and the regulations regarding Good Clinical Practice in the European Community (GCP) and in concordance with the current National Regulations. The protocol was reviewed and approved by the Medical Ethical Committee of Erasmus MC.

Materials and procedure

Visual emotional memory was tested using pictures from the International Affective Picture System (Lang, Cuthbert, & Attention, 2005). Two sets of 60 pictures each (20 neutral, 20 negative and 20 positive) were selected. The two sets were matched for valence and for content (same number of pictures featuring humans, animals, objects, etcetera) (see supplementary materials: list S1 for the stimuli). Mean male normative valence ratings were: set 1: neutral 5.05 (SD 0.51), negative 2.62 (SD 0.45), positive 7.08 (SD 0.63) and set 2: neutral 5.01 (SD 0.52), negative 2.62 (SD 0.58), positive 7.27 (SD 0.60). Subjects were seated in a well-lit soundproof room at approximately 60 cm distance from the 19' computer screen where stimuli were presented. Pictures were all resized to a size of 21.6° horizontally and 16.3° vertically. Tasks were programmed with "Presentation" 13.1 software (Neurobehavioral Systems). On day 1 participants were explicitly instructed to view 60 pictures and to remember as many pictures as possible for a memory test immediately after presentation and for a memory test the next day. Participants were not told that the test was designed to measure emotional memory modulation. Slides were presented for 4 seconds with a blank screen shown between the slides for 1 second.

Recall was tested immediately after presentation of the slides. Participants were required to verbally describe as many photographs as possible in 5 minutes with sufficient detail for the investigator to be able to identify the specific slide.

On day 2 recognition memory was tested. Participants were shown the 60 previously seen photographs and 60 new photographs in pseudo random order. For half the participants the photographs from set 1 were the targets and the photographs from set 2 were the distracters. For the others half of the participants set 2 were targets and set 1 were distracters. Participants were required to indicate whether they had seen the photograph the previous day by pressing one of two keyboard buttons. After each photograph, the stimuli were rated on the computer for valence and arousal using the 9-point Self Assessment Manikin (Bradley & Lang, 1994).

The same procedure was used to test verbal memory. Two lists of 60 words each (20 neutral, 20 negative and 20 positive), matched for affect rating and number of letters were selected from the list of words created by Hermans and Dehouwer (Hermans & Dehouwer, 1994).

Mean normative valence ratings on a seven point scale ranging from 1 "very negative" to 7 "very positive" were: list 1: neutral 4.03 (SD 0.27), negative 1.97 (SD 0.34), positive 5.85 (SD 0.26) and list 2: neutral 4.12 (SD 0.30), negative 1.96 (SD 0.32), positive 5.95 (SD 0.39). Words were presented in the Helvetica font with a size of 1.4° vertically and between 3.8° and 9.5° horizontally. On day one, participants passively viewed list 1 or 2 in pseudorandom order and were instructed to remember the words for the memory tests. Immediately after presentation there was a verbal recall test. On day two we performed a recognition test, in which the words from the other list were the distracters and all words were rated for valence and arousal using the 9-point Self Assessment Manikin immediately after presentation.

Statistical analyses

Valence and arousal ratings from ROS were compared to HC ratings by category of stimuli (neutral, negative and positive) using independent sample t-tests. Short-term memory performance was defined as percentage of correct free recall for verbal and visual stimuli. Signal detection models were used to analyze the long-term memory data. We calculated the A-prime score which takes into account the percentage of hits and false alarms (Stanislaw & Todorov, 1999). The formula for A-prime is: $0.5+((H-F)(1+H-F))/(4H(1-F))$ when $H \geq F$, and $0.5-((F-H)(1+F-H))/(4F(1-H))$ when $H<F$.

Statistical tests were performed using SPSS version 21 (PASW 2013). Data of stimulus ratings and memory performance were analyzed with mixed model repeated measurement ANOVA's. Significant effects were Huynh-Feldt corrected and further evaluated with post hoc T-tests. Significance level was set at 0.05.

To investigate the influence of clinical variables on test performance, we calculated Pearson correlation coefficients between overall long- and short-term visual and verbal memory performance and clinical variables. Significant correlations were followed up for the different emotional conditions.

Results

Valence and arousal ratings

There were no differences for valence ratings between HC and ROS (See also supplementary material table S1). Valence scores and standard deviations for visual stimuli were similar to the mean male normative valence ratings. HC rated the negative visual stimuli as more arousing than the ROS (ROS 5.01, HC 6.01, $t(3.090)$, $p=0.003$), for all other stimulus categories there was no difference between groups.

Table 1:Demographic and clinical data of participants

	Recent Onset Schizophrenia (SD)	Healthy Controls (SD)
n	45	37
Age (years)	23.3 (4.0)	23.1 (4.3)
Education (years) ***	7.3 (1.6)	8.7 (1.6)
DART IQ***	93.44 (8.6)	101.8 (8.5)
Raven IQ**	102.1 (17.2)	115.1 (18.9)
SWN***	83.3 (15.7)	96.5 (10.1)
PANSS total	58.5 (15.0)	
SANS	39.2 (21.8)	
SAPS	18.2 (15.5)	
Haloperidol equivalents	3.7 (3.5)	
Duration off illness (months)	14.8 (16.9)	

*** p < 0.01, *** p < 0.001*

Visual memory

We performed a mixed model repeated measurement ANOVA for percentage recalled stimuli in the STM task. As expected, ROS performance was below HC ($F(1,81)=42.272$, $p< 0.001$, $\eta2=0.346$). There was a main effect for emotion ($F(2,80)=23.428$, $p<0.001$, $\eta2=0.227$). Post hoc t-tests revealed that accuracy was better in both negative (0.38) and positive (0.38) compared to neutral stimuli (0.29, both $p < 0.001$), but no difference was found between positive and negative. There was no interaction between group and emotion.

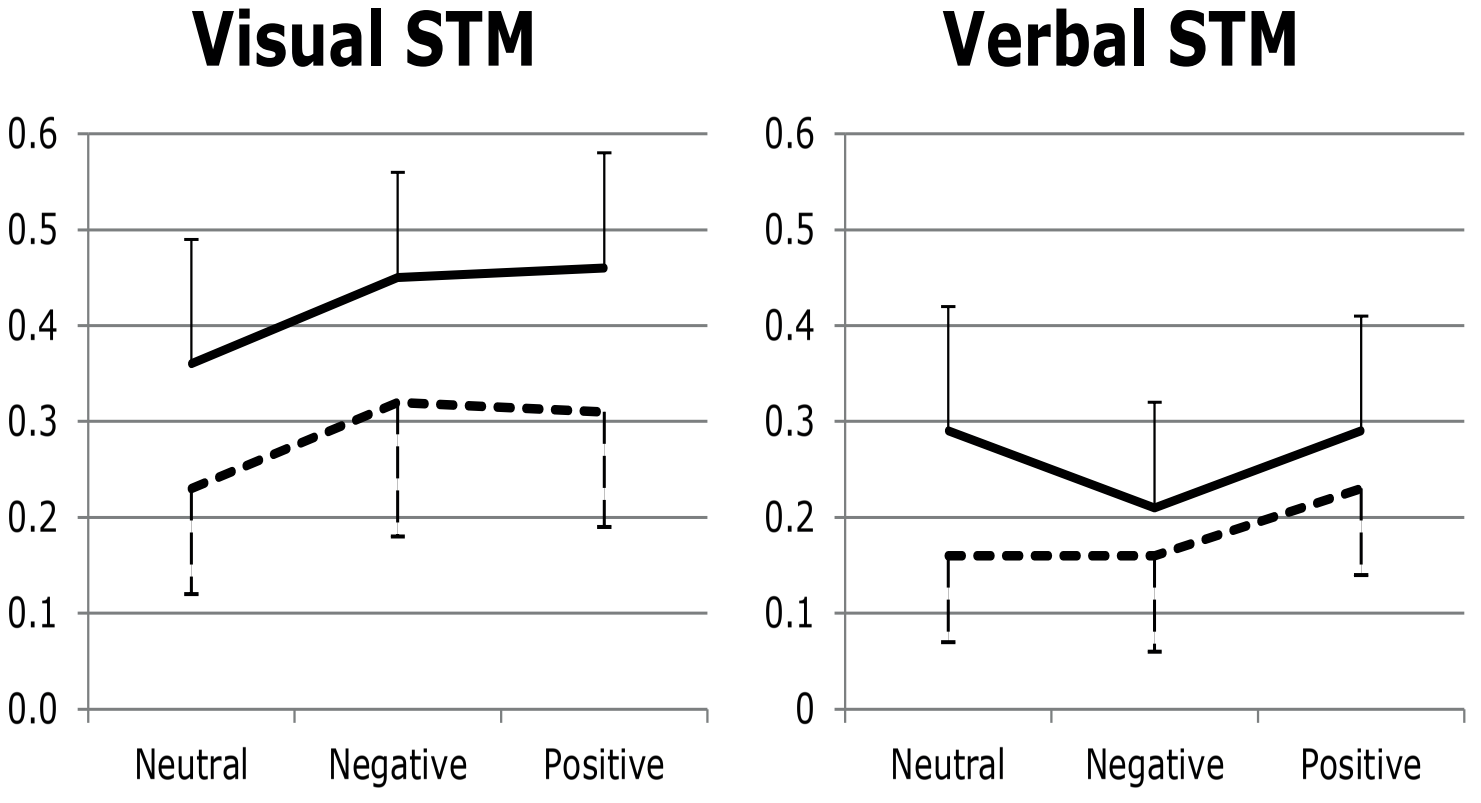
For visual long-term recognition we performed a similar ANOVA for A' values. ROS (0.84) performed worse than HC (0.93) ($F(1,81)=21.495$, $p<0.001$, $\eta2=0.212$). The emotion effect was also significant ($F(2,80)=12.974$, $p<0.001$, $\eta2=0.140$); performance on negative trials (0.90) was better than on neutral (0.88, $p=0.010$) and positive trials (0.86, $p<0.001$), but there was no difference between neutral and positive trials. There was no interaction between group and emotion.

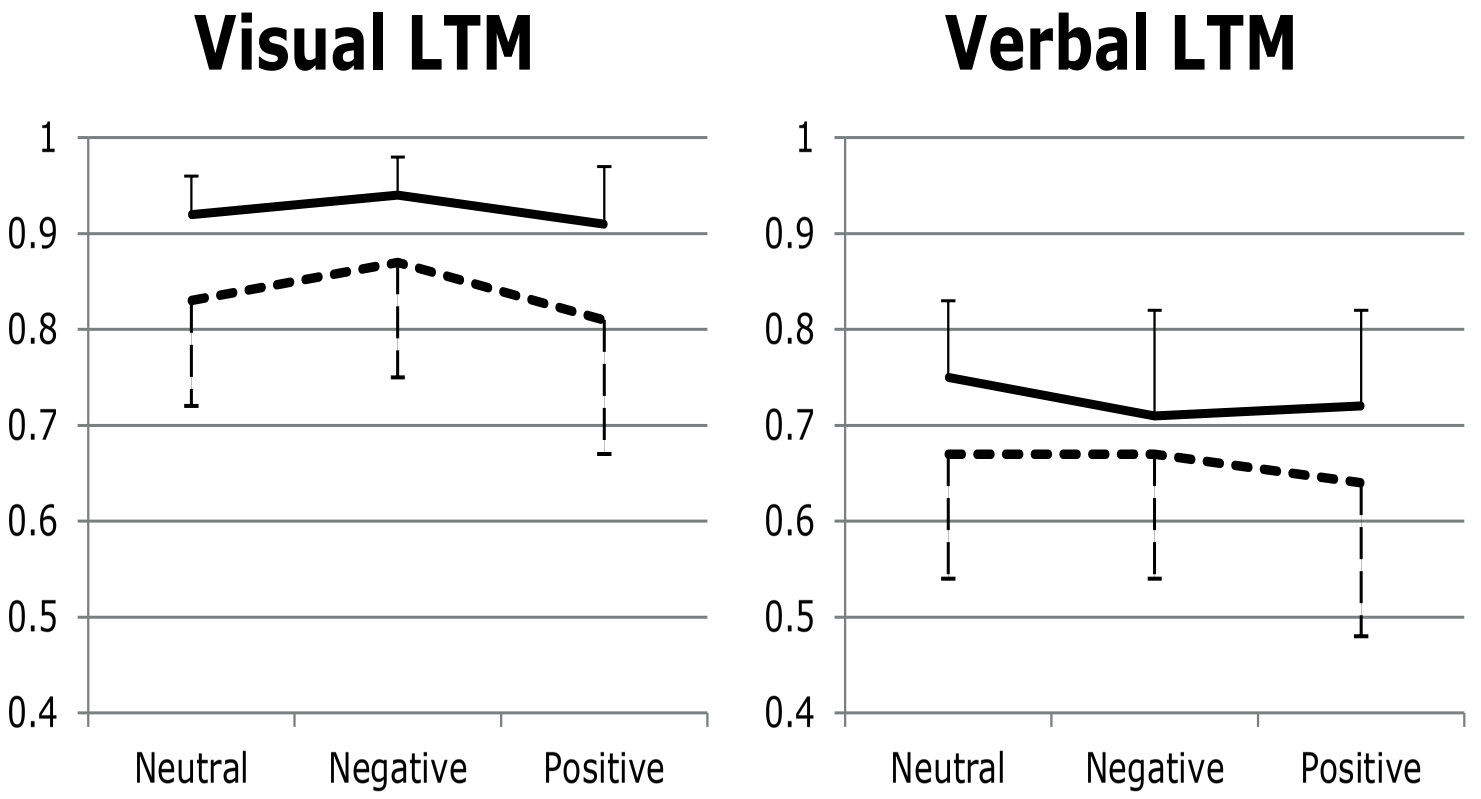
Verbal memory

We performed the same mixed model repeated measurement ANOVA as described for visual memory. In the verbal STM task ROS performed worse than HC ($F(1,81)=16.192$, $p<0.001$, $\eta2=0.168$). There was a main effect for emotion ($F(2,80)=5.609$, $p=0.009$, $\eta2=0.066$), post hoc t-tests revealed that accuracy was lower in negative (0.18) compared to positive (0.26, $p < 0.001$), but not compared to neutral words (0.22). There was no significant interaction between group and emotion.
ROS (0.66) performed worse on verbal LTM than HC (0.73)

Figure 1: performance on te different memory tasks

HC *ROS*





Performance for the different emotional conditions for healthy controls (HC) and first episode psychosis patients (FEP) for all experimental conditions. STM = short-term memory and features percentage correctly recalled stimuli, LTM = long term memory and features A-prime values.

(F(1,81)=10.718, p=0.002, η2=0.118). However for verbal LTM there was no emotion effect and no interaction between group and emotion.

Effect of stimulus type

To investigate the effect of stimulus type on STM, we performed a mixed model repeated measurement ANOVA with emotion and stimulus (verbal, visual) as within-subject variables and group as between-subjects factor for percentage recalled stimuli. Performance for visual (0.35) was better than for verbal (0.21) stimuli (F(1,81)=146.168, p<0.001, η2=0.646). There was also a main effect for emotion (F(2,80)=11.014, p<0.001, η2=0.121); performance on positive (0.32) was better than on neutral (0.26, p<0.001) and negative (0.28, p=0.001) trials, but the last two did not differ. We found a main effect for group (F(1,81)=38.075, p<0.001, η2=0.322). The emotion by stimulus interaction was significant (F(2,80)=11.174, p<0.001, η2=0.123). Visual STM performance was better in both negative (0.38) and positive (0.38) compared to neutral (0.29, both p<0.001) stimuli, verbal STM performance was lower in negative (0.18) compared to positive (0.26, p<0.001), but both did not differ from neutral words (0.22). There was no three-way interaction.

For LTM we performed the same ANOVA for A'. Again, performance for visual (0.88) was better than for verbal (0.69) stimuli (F(1,81)=254.702, p<0.001, η2=0.761) . The main effect for emotion (F(2,80)=5.649, p=0.004, η2=0.066.) was caused by worse performance on positive (0.77, both p<0.05) compared to negative (0.79) and neutral trials (0.79). The emotion by stimulus interaction was significant (F(2,80)=3.956, p=0.021, η2=0.047), for visual LTM performance on negative (0.90) was better than on neutral (0.88, p=0.010) and positive trials (0.86, p<0.001).For verbal LTM there were no differences between the three emotions. Again no three-way interaction was found.

Short vs. long-term

To compare short and the long-term visual memory we used hit rate instead of A' for LTM because it is more similar to percentage correctly remembered words used in the STM task. We performed a repeated measurement ANOVA with emotion and delay (STM, LTM) as within-subject variables and group as between-subjects factor for percentage recalled stimuli. A main effect for delay was present (F(1,81)=597.998, p<0.001, η2=0.882). The interaction between delay and group was also significant (F(1,81)=4.806, p=0.031, η2=0.057): the increase in performance for LTM compared to STM is larger in HC than in patients with schizophrenia. We found no interaction between emotion, delay and group. We used the same procedure for verbal memory and found a main effect for delay (F(1,81)=231.468, p<0.001, η2=0.743). The interactions between delay and group and between delay, group and emotion were not significant.

Finally, a repeated measurement ANOVA with emotion (neutral, negative and positive), stimulus (verbal, visual) and delay (STM, LTM) as within-subject variables and group (HC, ROS) as between-subjects factor

was performed. There was an interaction between delay, stimulus and emotion ($F(2,80)=14.181$, $p<0.001$, $\eta 2=0.151$), showing that the way emotion modulates memory, depends on both stimulus type and delay as can be seen in figure 1. There was, however, no interaction between group and delay, stimulus and emotion; there is no difference between ROS and HC in the way emotion modulates different memory domains.

Correlations

In the ROS group we found a correlation between SANS total score and visual STM (-.473, p=0.001). When this correlation was followed-up for the different emotional conditions, we found a correlation between SANS score and neutral (-.386, p=0.010) and positive (-.485, p=0.001), but not negative stimuli. There was no correlation between performance and either DART IQ, Raven IQ, SWN, Haloperidol equivalent, PANSS total score and SANS score.

Discussion

We investigated the influence of emotion on short- and long-term verbal and visual memory in patients with recent onset schizophrenia compared to healthy controls. We found that on all tasks overall performance for ROS was significantly below that of healthy controls. There were differences between the tasks in the way emotion modulated memory performance, but emotional memory modulation did not differ between ROS and HC.

The overall memory impairments are in line with previous findings in first-episode psychosis patients (Mesholam-Gately et al., 2009). Several studies have shown deterioration in verbal and visual memory function in the first three or four years after the first-episode psychosis (Frangou, Hadjulis, & Vourdas, 2008; Rodriguez-Sanchez et al., 2013). Although we measured valence and arousal a day after the first presentation of the stimuli, the results are in line with previous studies that demonstrated that patients with schizophrenia have intact in-the-moment emotions when presented with different types of emotional stimuli (Herbener, 2008), although there is evidence that patients with schizophrenia cannot keep them over longer time periods (Kring & Moran, 2008).

There were no impairments in EMM in ROS for both STM and LTM. Similar EMM in patients with schizophrenia despite a general memory deficit have been reported previously (e.g. Harvey, Bodnar, Sergerie, Armony, & Lepage, 2009; Sergerie, Armony, Menear, Sutton, & Lepage, 2010; Whalley et al., 2009), but there are also contradictory results (e.g. Herbener et al., 2007; Lakis et al., 2011; Neumann et al., 2007). In chapter 5 we concluded that these differences could be caused by different study designs, therefore we examined STM and LTM in the same group. However, we found no effects of delay on EMM. Contrary to Herbener et al. (Herbener et al., 2007) who found that positive stimuli did not enhance memory in patients with schizophrenia like in healthy controls in visual

LTM, we found no difference in emotional visual LTM modulation. However, Herbener et al. (Herbener et al., 2007) examined chronic schizophrenia patients. This suggests that deficits in emotional memory modulation debut further down the course of the disease.

We found differences in the increase of memory performance between STM and LTM in the two groups with respect to visual but not verbal stimuli. The increase in performance in HC was significantly bigger than in patients. This supports the hypothesis, that in patients with schizophrenia the consolidation process is impaired. However, the impairment seems more prominent in the visual domain. Previous studies reported differences in EMM between STM and LTM (Calev & Edelist, 1993; Hall et al., 2007). EMM was similar in HC and patients for STM. For LTM reduced EMM in patients with schizophrenia compared to HC was reported for positive stimuli in both studies, but for negative stimuli only by one (Hall et al., 2007). Both studies examined chronic patients and included less participants than our study. This suggests, that although ROS already have emotional and memory impairments, these impairments only interact later in the course of the disease. Another explanation could be that Hall et al. (2007) did not use explicit memory instructions and found deficits in EMM because patients with schizophrenia have deficits in automatically using emotional content to enhance memory (Ranganath, Minzenberg, & Ragland, 2008 and chapter 5).

Several studies have linked emotional memory deficits to negative symptoms (Calev & Edelist, 1993; Hall et al., 2007) but only for long term memory. We found a correlation between negative symptom score and neutral and positive but not negative visual STM. A possible interpretation is that negative symptoms impair the experience of positive and neutral emotions and not negative emotions, because when patients suffer from more negative symptoms, they find it harder to disengage attention from negative stimuli (Strauss, Llerena, & Gold, 2011). However, this does not lead to a difference in EMM between HC and ROS. Furthermore, most studies found no correlation with either positive or negative symptoms (chapter 5).

Limitations

Due to the heterogeneity in medication use it was not possible to compare different antipsychotics. Although the inclusion of only male first episode patients may make our results less generalizable to patients suffering from schizophrenia in general, it makes them more specific to a large part of the patients usually included in first episode schizophrenia programs.

Due to the broad research questions addressed in this study, we cannot exclude possible interference between the results in the four different memory domains. The STM recall of stimuli that had to be remembered creates a learning effect for these stimuli, making them easier to remember than the stimuli that were not recalled. It is also possible that the consolidation processes for verbal and visual stimuli interfered with

each other and thereby diminished a possible EMM effect. This is inherent to the present research question and furthermore it is important to notice that there were effects of emotion and these did not differ between ROS and HC.

Conclusion

We investigated the influence of emotion on short and long-term verbal and visual memory in patients witch recent onset schizophrenia compared to healthy controls. We demonstrated that although the way emotion modulates memory depends on both stimulus type and delay, there is no difference between ROS and HC in the way emotion modulates different memory domains.

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Supplementary materials: list S1

IAPS pictures Set 1:
Negative:
2800(sad child), 3030(mutilation), 3101(burnt face), 3181(battered female), 3230(dying man), 3266(injury), 3300(disabled child), 3530(attack), 6260(aimed gun), 6350(attack), 9000(cemetery), 9182(horses), 9250(war victim), 9320(vomit), 9433(dead man), 9520(kids), 9584(dental exam), 9620(shipwreck), 9810(KKK rally), 9920(car accident)
Neutral:
1240(spider), 2190(man), 2210(neutral face), 2372(woman), 2487(musician), 2520(elderly man), 2594(city), 2840(chess), 4571(attractive man), 4605(couple), 5500(mushroom), 6150(outlet), 6900(aircraft), 7004(spoon), 7009(mug), 7025(stool), 7060(trash can), 7211(clock), 7351(pizza), 7495(store)
Positive:
1440(seal), 1463(kittens), 1603(butterfly), 1610(rabbit), 2000(adult), 2070(baby), 2165(father), 2340(family), 4220(erotic female), 4599(romance), 4610(romance), 5593(sky), 5660(mountains), 5760(nature), 5831(seagulls), 7340(ice cream), 7352(pizza), 7480(pasta), 8380(athletes), 8501(money)

IAPS pictures Set 2:
Negative:
2900(crying boy), 3100(burn victim), 3170(baby tumor), 3180(battered female), 3220(hospital), 3280(dental exam), 3301(injured child), 3350(infant), 3550(injury), 6230(aimed gun), 6313(attack), 9001(cemetery), 9040(starving child), 9140(cow), 9300(dirty), 9341(pollution), 9410(soldier), 9600(ship), 9800(skinhead), 9911(car accident)
Neutral:
1230(spider), 2200(neutral face), 2383(secretary), 2410(boy), 2435(mom/son), 2495(man), 2518(quilting), 2850(tourist), 4572(attractive male), 5534(mushrooms), 6910(bomber), 7035(mug), 7080(fork), 7150(umbrella), 7190(clock), 7235(chair), 7283(fruit), 7496(street), 7595(traffic), 7705(cabinet)
Positive:
1460(kitten), 1604(butterfly), 1710(puppies), 1750(bunnies), 2010(adult), 2160(father), 2260(neutral baby), 2311(mother), 4250(attractive female), 4608(erotic couple), 4700(couple), 5200(flowers), 5700(mountains), 5780(nature), 5891(clouds), 7230(turkey), 7330(ice cream), 7470(pancakes), 8502(money), 8540(athletes)

Words List 1:
Negative:
BAZIG (bossy), BRUTAAL (cheeky), DRUGS (drugs), HAAT (hate), KANKER (cancer), KLAGEND (plaintive), LAF (cowardly), LASTIG (difficult), MISDAAD (crime), ONGEVAL (accident), PANIEK (panic), PIJN (pain), SCHADE (damage), SCHULD (guild), VET (fat), VREES (fear), VUIL (dirty), VUILNIS (trash), WREED (cruel), ZORGEN (worries)
Neutral:
BIER (beer), BRIL (glasses), DANCING (disco), DISCO (disco), GEK (crazy), GEWETEN (conscience), KAPPER (hairdresser), KRANT (newspaper), LETTER (letter), STEEN (rock), STREEP (stripe), TAFEL (table), TAS (bag), TIMIDE (timid), TOILET (toilet), VENSTER (window), VERBAND (bandage), VOETBAL (soccer), WINTER (winter), WOLK (cloud)
Positive:
ACTIEF (active), ATTENT (thoughtful), BABY (baby), BAD (bath), BED (bed), BEKWAAM (capable), BLOEMEN (flowers), FEEST (party), FILM (movie), HEMEL (heaven), HONDJE (dog), HUMOR (humor), LOYAAL (loyal), OPRECHT (sincere), ORGASME (orgasm), SEKS (sex), TACTVOL (tactful), TROUW (loyalty), WARMTE (heat), ZUIVER (pure)

Words List 2:
Negative:
AFKERIG (averse), AFVAL (waste), AIDS (aids), ANGST (fear), DOOD (dead), DRIFTIG (hot-spirited), EXAMENS (exams) GEMEEN (mean), KOORTS (fever), KWAAD (evil), MONSTER (monster), ONECHT (fake), ONGELUK (accident), PUIST (pimple), RODDEL (gossip), RUW (rude), STANK (stench), VALS (mean), VULGAIR (vulgar), ZIEKTE (disease)
Neutral:
AUTOBUS (bus), BOTER (butter), BROEK (trousers), DOOS (box), ERNSTIG (serious), GEHEIM (secret), GELATEN (subdued), KEEL (throat), KLAS (class), MODIEUS (fashionable), NEDERIG (humble), PAPIER (paper), RAADSEL (riddle), ROK (skirt), SCHAAR (scissors), SCHOOL (school), STIER (bull), STOEL (chair), STOEP (sidewalk), VAGINA (vagina)
Positive:
BLOESEM (blossom), BOEKET (bouquet), BRIEF (letter), BRUID (bride), CADEAU (gift), HOOPVOL (hopeful), KIND (child), KNUFFEL (hug), LENTE (spring), LIEFDE (love), MELODIE (melody) ,MOEDIG (brave), POESJE (kitten), ROOMIJS (ice cream), SOCIAAL(social), VREDE (peace), WENS (wish), WIJS (wise), ZOMER (summer), ZON (sun)

Supplementary materials: table S1 Valance and arousal ratings

	Valence				*Arousal*			
	HC	*SD*	*ROS*	*SD*	*HC*	*SD*	*ROS*	*SD*
Visual								
Neutral	*5.09*	*0.47*	*4.88*	*0.99*	*4.02*	*0.99*	*3.99*	*1.52*
Negative	*2.66*	*0.69*	*2.76*	*1.20*	*6.01***	*1.20*	*5.01***	*1.73*
Positive	*6.38*	*0.58*	*6.24*	*0.83*	*5.45*	*0.88*	*5.08*	*1.20*
Verbal								
Neutral	*5.32*	*0.55*	*5.20*	*0.70*	*4.54*	*1.03*	*4.57*	*1.11*
Negative	*3.26*	*0.67*	*3.44*	*0.93*	*5.40*	*1.17*	*4.97*	*1.22*
Positive	*6.78*	*0.60*	*6.56*	*0.91*	*5.92*	*0.78*	*5.71*	*0.98*

*** p < 0.01*

Chapter 7

Impairment of gaze-directed spatial coding in recent onset schizophrenia

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Abstract

Patients with schizophrenia show deficits in core cognitive functions as well as in social cognition. The aim of the present study was to test whether deficits in social cognition influence non-social, "cold", cognition. Thirty-five patients with recent-onset schizophrenia (SC) and thirty healthy controls (HC) performed a Simon task with social and simple geometric stimuli. We investigated whether the Simon effect, the slowing of reaction times produced by stimulus incongruities in the task irrelevant spatial domain, differs between patients and healthy participants as a function of the social nature of the cues. The Simon-effect was generated by a schematic drawing of human eyes (social cues) or rectangles (non-social cues). Overall, patients had longer reaction times than HC. In the eye-like condition, the Simon-effect was significantly stronger for HC than SC. In HC the Simon-effect was significantly stronger in the eye-like compared to the rectangle condition. In patients, the Simon effect did not differ significantly between both conditions. Thus, the influence of social cues was greatly reduced in the patient group. Current psychopathology or antipsychotic treatment did not influence results. The present study supports earlier findings of altered processing of schematic social cues in patients with schizophrenia, especially when gaze is task-irrelevant.

Introduction

Schizophrenia is a psychiatric illness, which is characterised by "positive" symptoms such as delusions, hallucinations and disorganization on the one hand and "negative" symptoms such as lack of drive, reduction in hedonic experience and social withdrawal on the other. In addition, many patients suffer from cognitive deficits such as impairments in selective attention (Krieger et al., 2005), perception (Sergi & Green, 2003), speed of processing (Bechard-Evans, Iyer, Lepage, Joober, & Malla, 2010), and working memory (Haenschel et al., 2007). More recently, deficits in social cognition, for example emotional processing, social perception, attributional bias and theory of mind, have become a focus of schizophrenia research (Green & Horan, 2010). Brothers (Brothers, 2002) defined social cognition as "the processing of any information which culminates in the accurate perception of the dispositions and intentions of other individuals". It is an on-going debate to what extent general cognitive abilities and social cognition overlap. In healthy subjects Ziv, Leiser and Levine (2011) identified two independent factors for core cognition and social cognition and found that deficits in social cognition could not be entirely attributed to deficits in executive functioning. Similarly, social cognition deficits in patients with schizophrenia only partially explained by deficits in core cognitive functions (Brune, 2005; Ziv et al., 2011). Although performance on general cognitive tests explained a high percentage of variance in social cognitive tasks in patients with schizophrenia (Sergi et al., 2007; Vauth, Rusch, Wirtz, & Corrigan, 2004), a model with two separate factors fitted the data better, than a model with a combined factor for both domains (Sergi et al., 2007). More recently, van Hooren et al. (2008) concluded that core cognition and social cognition are two separate domains in patients with schizophrenia. They further suggest, that the concept of social cognition as a coherent domain is problematic, as the different domains of social cognition comprise various independent cognitive mechanisms (van Hooren et al., 2008). Furthermore, a recent meta-analysis found only small to moderate correlations between social cognitive domains and the non-social cognitive domains of the MATRICS (Ventura, Wood, & Hellemann, 2013).

Previous studies have mainly focused on potential influences of general cognitive abilities on social cognition. Whether altered social cognition in turn influences "cold" cognition in schizophrenia is largely unknown (Bustillo et al., 1997). Gaze is the quintessential social cue (Shepherd, 2010), which may inform about other individuals' intentions. The position of body, head and the orientation of eyes can direct spatial attention or social gaze. The importance of eye gaze compared to head or body position is emphasized by the hierarchical organization of the brain areas subserving these functions. Neurons coding for eye gaze can inhibit neurons coding for averted head position, and information about head position can inhibit neurons coding for averted body position (Perrett, Hietanen, Oram, & Benson, 1992).

Several studies found that the perception of gaze deviation (Franck et al., 1998; Franck et al., 2002; Hooker & Park, 2005; Tso, Mui, Taylor, & Deldin, 2012) is similar in patients with schizophrenia and healthy controls for gaze that is averted to the left or right. However, patients with schizophrenia have the tendency to interpret slightly averted gaze as directed to them (Hooker & Park, 2005) and to perceive gaze as directed to them earlier than healthy controls when gaze is rotated in a stepwise fashion towards the observer (Tso et al., 2012). Patients who have a stronger tendency to perceive gaze as directed to them were more impaired in socio-emotional functioning (Tso et al., 2012).

Gaze cueing describes the effect of the gaze of another person on spatial attention (Driver et al., 1999).Gaze cueing is already present in three month old or even younger infants (Hoehl et al., 2009), and can also be evoked by schematic pictures of eye-like objects. It has been shown in multiple studies (for an overview see (Tipper, 2010)) that this effect is measurable by faster reaction times to stimuli presented in the attended space compared to stimuli presented in the unattended space, even when gaze is not predictive (Frischen & Tipper, 2004). These results and the fast occurrence of the cue effects (within 200 ms of gaze shift) indicate an automatic, reflexive and stimulus-driven (exogenous) orienting of attention, which is impossible to suppress.

Gaze cues can be effective in guiding or disrupting attention (Tipper, 2010), but only few studies have studied this process in patients with schizophrenia (Akiyama et al., 2008a; Langdon, Corner, McLaren, Coltheart, & Ward, 2006; Magnee, Kahn, Cahn, & Kemner, 2011) with diverging results. Langdon et al. (2006) and Magnee et al. (2011), found no differences between patients with schizophrenia and healthy controls: patients had even better cueing effects at very short stimulus-onset-asynchrony (SOA) of 100 ms than healthy controls (Langdon et al., 2006). In contrast, chronic patients with schizophrenia profited less from gaze cueing with schematic eyes than healthy controls (Akiyama et al., 2008b), while both groups show similar results when arrows are used as spatial cues (Magnee et al., 2011). The biggest differences between patients with schizophrenia and healthy controls were observed when abstract symbols were used to cue spatial attention (Akiyama et al., 2008b). However all three studies used different stimuli, which may account for the diverging results. Langdon et al. (2006) presented faces, which were either turned to the left or right, thus gaze in a narrow sense was not examined. Magnee et al. (2011) presented frontal faces with deviated and neutral gaze. Akiyama et al. (2008b) used two different stimuli categories, one of which one resembled eyes. Stimuli were derived from an earlier study examining spatial coding of the Simon effect (Zorzi, Mapelli, Rusconi, & Umilta, 2003).

Effects of gaze shift have been further examined in patients with schizophrenia using the inhibition of return (IOR)-paradigm (Carter, Robertson, Chaderjian, O'Shora-Celaya, & Nordahl, 1994; Gouzoulis-Mayfrank et al., 2007; Nestor, Klein, Pomplun, Niznikiewicz, & McCarley,

2010). Inhibition of return describes the observation that a lateralized cue presented more than 300 ms before a subsequent target stimulus at the same location increases reaction time. In contrast, time intervals between cue and target stimulus smaller th an 300 ms facilitate reaction times. Inhibition of return has been characterized as a fundamental mechanism of perception which serves the orientation of attention to novel objects in the environment (Posner & Cohen, 1984). Patients with schizophrenia had similar performance as healthy controls (Nestor et al., 2010) when geometrical stimuli were used as cues. When gaze was used in order to direct attention, healthy controls still demonstrated IOR, but patients with schizophrenia had shorter reaction times to stimuli in the cued hemifield after a time gap of more than 2000 ms (Nestor et al., 2010). However, other studies found impairments of IOR in patients also for geometrical stimuli (Carter et al., 1994; Gouzoulis-Mayfrank et al., 2007). Thus, summarizing the findings from the presented studies, patients with schizophrenia processed gaze similarly to healthy controls only under some experimental conditions.

In the previously described studies, a non-informative lateralized cue preceded a lateralized target stimulus. In contrast, the Simon task requires a response to a laterally presented stimulus, but the spatial property of the stimulus is task irrelevant (Simon & Rudell, 1967; Simon & Small, 1969). Faster and less error-prone responses are obtained when the task-irrelevant stimulus location and the response are on the same side rather than on opposite sides (congruency effect). A standard procedure for eliciting the Simon effect utilises visual stimuli presented laterally and a non-spatial stimulus dimension such as colour (e.g., red vs. green) or shape (e.g., circle vs. square) that demands forced choice responses with the left or right hand (Aisenberg & Henik, 2010; Tagliabue, Umilta, & Spera, 2009). Thus, the classical Simon task primarily examines cognitive control processes, in which stimulus-response incompatibility is examined.

Different theories have been proposed to explain the Simon effect. Kornblum (1994) suggested an overlap between the irrelevant stimulus feature and the response set, where the irrelevant stimulus feature (left-right) activates its corresponding element of the response set. However, the activated response must be identified as correct or incorrect, and the theory assumes that identity of activated and correct response consume less time than the case when activated and correct response are not identical. Others have suggested that the Simon effect is caused by spatial coding, an attentional process (Nicoletti & Umilta, 1994; Proctor & Lu, 1994; Stoffer & Yakin, 1994). Spatial coding is explained by a planned execution of a saccade to the location where the stimulus appears (Nicoletti & Umilta, 1994). In this model, attention shifts to the location where the stimulus appears which results in facilitation for stimuli corresponding to the response and interference for stimuli not corresponding to response. Another theoretical proposal (Barber & O'Leary, 1997) suggested that an automatic activation to respond to the irrelevant stimulus feature (spatial

location) interferes with task instruction to react to the relevant feature (colour).

The more recent theory of event coding suggests that the mental representation of stimuli (perceived event) and responses (produced events) are coded in a similar way (Hommel, 2011). With respect to the Simon task, both stimulus features, i.e. colour and location, form a stimulus event, and both the movement and its perceptual consequences form the produced event. As a consequence, the partial overlap between the irrelevant stimulus property (perceived event) and the lateralized response (produced event) would facilitate response to congruent events .

We designed the present study specifically to enable us to rule out some of the factors proposed by existing theories. Bilateral presentation of stimuli prevents an overlap between irrelevant stimulus feature and response set (Kornblum, 1994), an automatic activation to respond to the irrelevant stimulus feature (Barber & O'Leary, 1997), or an overlap between perceived and produced event (Hommel, 2011). Thus, we mainly rely on the theory of spatial coding, relevant for the possible observed Simon effect, which could also examines the effect of social stimuli on the Simon effect.

In order to bring a social component into the Simon task, Zorzi et al. (2003) introduced a combination of gaze cueing. Contrary to the standard Simon task the stimuli in this version are not displayed in one of the visual hemifields, but two identical stimuli are presented, one in each hemifield. Two types of stimuli are used, a coloured square surrounded by a rectangle and a coloured circle surrounded by an ellipse, the latter resembling eyes, and participants have to react to the colour of the stimuli with either the right or left hand. The authors systematically varied the location of the inner part of the stimulus (square or circle) across three positions, either in the middle or near either side of the outer shape (rectangle or ellipse) (see figure 1). They described a "gaze directed Simon effect" (Zorzi et al., 2003), which was owed to the spatial coding by gaze shift, but could only be induced with eye-like stimuli, confirming earlier findings (Friesen & Kingstone, 1998). Thus, this design may rely less on cognitive control mechanisms as the classical Simon task than on spatial coding.

Akiyama et al. (2008b) recently used gaze-direction cues in a spatial orienting task in a group of patients with chronic schizophrenia. In contrast to Zorzi et al. (2003), stimuli were presented in black and white and were used as cues for subsequently presented target stimuli presented in the left or right hemifield, to which participants were asked to react. Thus, Akiyama et al. (2008b) did not examine the Simon effect but spatial attention. In patients with schizophrenia the eye-like stimuli caused a trend level decrease of reaction time, but the rectangle condition caused no significant congruency effect. In contrast, healthy controls demonstrated significant congruency effects for all both conditions (arrows, rectangles and eye-like stimuli).

In contrast to the standard design of the Simon task, the design of Zorzi et al. (2003) also allows to examine whether the Simon effect is caused by interference or facilitation. The aim of the present study was to investigate the extent to which social cues influence the attention of patients with recent onset schizophrenia (SC). We used the same design as Zorzi et al. (2003) to examine whether patients with schizophrenia are able to use the eye-like stimuli in the same way as healthy controls (HC). Secondly, we wanted to replicate their results in a larger sample of healthy subjects. We hypothesized that patients would show a smaller Simon effect with the social (gaze) cues compared to healthy controls.

Material and Methods

Participants

We compared a group of 35 male recent-onset (defined as duration of illness < 5 yr) patients with schizophrenia (Mage = 23.5 years, SD 3.9) with a group of 30 male healthy control subjects (Mage = 24.4 years, SD 3.4) matched for age ($t(63 = 0.753$, $p = .306$). We decided to include only male subjects because of gender differences in attentional cueing following the presentation of averted eyes (Bayliss, di Pellegrino, & Tipper, 2005). All participants were right-handed as evaluated with the Edinburgh Handedness Inventory (Oldfield, 1971). Mean of duration of illness was 16.4 months (SD 9.7 months). Two patients were excluded from further analysis because their mean reaction times were more than 2 standard deviations above the mean of the patient group. All patients were or had been hospitalized in our department at the time of testing and all were diagnosed according to DSM-IV criteria. Diagnoses were made by clinical consensus amongst clinicians highly experienced in working with patients with psychosis and was confirmed from case-notes using OPCRIT criteria (McGuffin, Farmer, & Harvey, 1991). Patients with duration of symptoms of less than 6 months at time of examination were reassessed after 6 months to comply with the DSM-IV criteria. We defined beginning of schizophrenia either as the time of occurrence of positive symptoms or as the occurrence of clear limitations in social or occupational functioning, if these latter symptoms were the first to emerge. As a consequence, this method yields a relatively long duration of illness when compared with assessing only positive symptoms. None of the healthy volunteers met criteria for a current diagnosis or a history of any axis I disorder, serious somatic disorder or any cerebral trauma as assessed by questionnaire and personal interview. We did not include control participants with a first-degree relative with a history of psychosis or any other serious psychiatric disorder.

Because of the frequent methodological problems when trying to match SC with HC on variables such as education or intelligence (Meehl, 1970), we decided not to try to match HC with patients on level of education. Due to the specific circumstances of our patient population with a high percentage of second-generation immigrants, measures of

socio-economic status or education of parents would not represent correctly possible differences in intelligence. All participants read the study information sheet and gave informed consent. The study was approved by the Medical Ethics Board of the Erasmus MC, Rotterdam.

10 of the patients were free of medication (3 of them naïve) for at least 4 weeks, all other were on a stable dose of medication (clozapine n=7, cyclopentixol n=2, haloperidol n=6, olanzapine n=4, quetiapine n=1 and risperidone n=3) for at least 4 weeks. Individual dose of medication was calculated in chlorpromazine (CPZ) equivalents. Actual psychopathology was rated with the Positive and Negative Symptom Scale (PANNS) (Kay, Fiszbein, & Opler, 1987) at the day after testing. Extrapyramidal symptoms were scored using the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard & Margolese, 2005).

Materials and Procedure

We used an adapted version of the Simon task (Zorzi et al., 2003) (see figure 1). A series of stimuli were presented to subjects, either with neutral gaze or gaze to the left or right. Stimuli were either in blue or green. Participants were instructed to react to the colour of the stimuli, irrespective of position by pushing a button with the right hand for one colour and with the left hand for the other. The colour-response hand allocation was balanced over subjects for the two colours. Participants were instructed to push as fast as possible when the stimulus appeared on the computer screen, which stayed on the screen until a response was given. Stimulus presentation was controlled by E-Prime 1.1.4, running on a personal computer. Participants were seated in front of a 17-inch screen at a distance of 60 cm. Reaction times and correct/incorrect responses were recorded and went into further statistical analysis.

We used two different stimuli. In the first condition, subjects saw a fixation cross (0.7°x0.7°) in the middle of the screen. The overall size of the stimulus was 20° and comprised a square with a size of 2° surrounded by a rectangle of 8.6° at both sides of the fixation cross. The squares were always kept in position, but the rectangles could be displayed in three different positions. The neutral position left the square in the centre of the rectangle, for spatial coding to the left the rectangle was moved to the right and for spatial coding to the right the rectangle was moved to the left. The square was either blue or green. Half of the subjects had to push a button with the right hand for blue and with the left hand for green, for the other participants the buttons were the other way around. The stimuli stayed until a response was given. Each trial ended with an intertrial-interval of 1000 ms. In total 180 trials had to be performed, 90 with green squares and 90 with blue squares. For each position (neutral, left, right) of the square within the rectangle 60 trials were presented. Before testing subjects performed a short practice with 20 trials to get accustomed to the task. The second condition kept the same paradigm except the shape of the stimuli. Instead of squares, small filled circles with a size of 3.8° were placed surrounded by an ellipse of 8.6° horizontal and 4.6° vertical

Table 1: Demographic and clinical characteristics of patients and controls. For statistical details, see demographics in the result sections.

	Healthy Controls		Patients with Schizophrenia: all		Patients: medicated		Patients: unmedicated	
	n=30		n=33		n=23		n=10	
	mean	range	mean	range	mean	range	mean	range
Age (years)	24.4	18 - 34	23.7	18 - 33	24.2	18 - 33	23.5	17 - 30
	mean	SD	mean	SD	mean	SD	mean	SD
Years of education	11.9	0,37	10.5	0.79	10.7	0.73	10.4	.9
Duration of ilness (month)			22	15.8	24.5	15.6	14.8	14.9
PANSS			mean	SD	mean	SD	mean	SD
Positive			11.6	6.9	9.4	6.1	16.8	5.7
Negative			15.7	8.2	15.1	9.3	17.0	4.9
General			26.7	12.3	23.5	12.6	33.9	8
Total			53.9	25	48	26.1	67.7	16.3
Medication							CPZ-eqivalents	
						n	mean	SD
Clozapine						7	423.3	107.5
Cyclopentixol						2	275.0	35.4
Haloperidol						6	276.7	65
Olanzapine						4	150	70.1
Quetiapine						1	640.0	
Risperidone						3	275	43.3
					total	23	314.7	138.8

in size. It has been reported earlier in normal subjects (Zorzi et al., 2003) that these stimuli were perceived as eyes. Similar to the first condition, the ellipse could be displayed in three different positions, neutral with spatial coding to the left or spatial coding to the right. The order of the two blocks was fixed, with control stimuli always presented before the eye-like stimuli. This procedure was specifically designed to avoid a carry-over effect of the eye-like stimuli on the control stimuli. That is, seeing the eye-like stimuli first would produce a strong tendency to perceive the squares as eyes.

Statistics

All reaction times (RT) and number of errors were recorded. Only RTs of correct answers were entered into further analysis. Mean RTs for each condition (neutral, corresponding, non- corresponding) in both tasks (rectangles, eyes) for each subject were calculated. RT of each subject that differed more than three standard deviations from the mean of the subject were excluded from further analysis. For testing of normal distribution, we performed a Kolmogorov-Smirnov-test on all raw data. In several patient groups higher intra-individual variability has been described (Klein, Wendling, Huettner, Ruder, & Peper, 2006), which may influence significance of results compared to healthy controls. We therefore compared also the individual standard deviation of overall reaction times. Because longer reaction times, typically found in patients with schizophrenia, also leads to numerically higher standard deviation we calculated the intra-individual coefficient of variance by dividing the intra-individual standard deviation by the individual mean reaction time (Wagenmakers & Brown, 2007). Both were compared with t-test between the two groups.

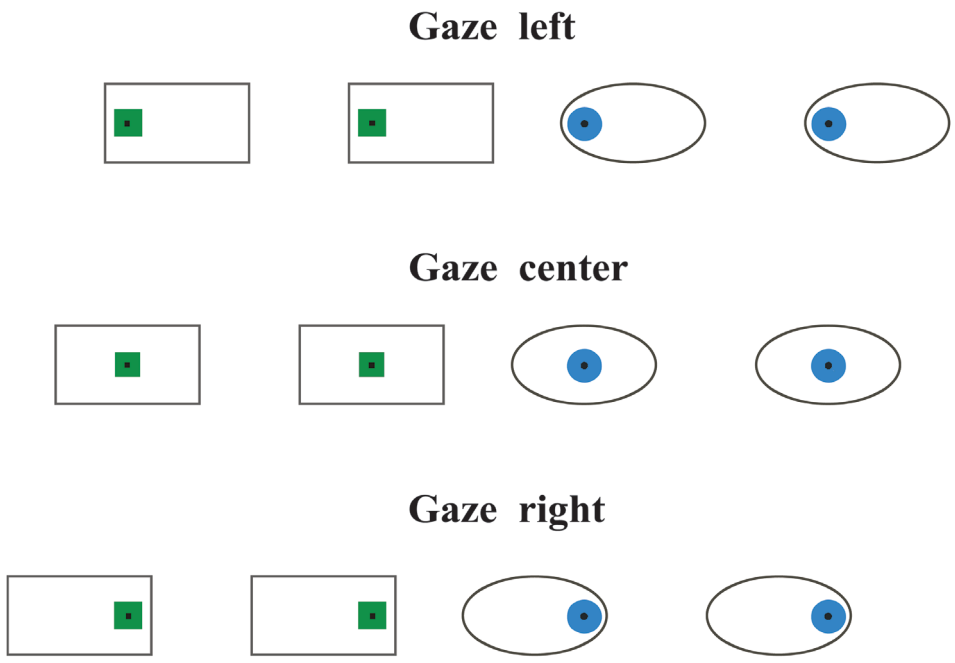
First, we compared medicated (SC_med) and unmedicated (SC_unmed) patients with a mixed-design ANOVA with the factor group (SC_med vs. SC_unmed) as between-subject-factor and condition (rectangle vs. eye) and congruency (congruent, neutral, incongruent) as within-subject-factors. Secondly, we performed the same mixed-design ANOVA with patients (SC) and healthy controls (HC) as between subject factor. Subsequently we calculated the Simon effect by subtracting the congruent condition from the incongruent condition for both task conditions separately. Again, we calculated two mixed design ANOVAs with Simon effect as within-subject factor and group (1.:SC_med vs. SC_unmed; 2.: HC vs. SC).

We finally examined the facilitation and interference effects of spatial coding by calculating the differences between neutral and congruent and incongruent and neutral trials of each subject for the rectangle and the eye-condition separately. As before results were initially analysed for the two patient groups and subsequently for the total group of patients with a mixed design ANOVA with condition (rectangle vs. eye) and facilitation vs. interference as within-subject factors.

Significant interactions were further analysed with post-hoc t-tests. When necessary, nonparametric tests were used. To evaluate

possible effects of psychopathology and medication we correlated results with psychopathology and CPZ-equivalents. In addition, we correlated results in the patient group with level of education. All ANOVA-results were Greenhouse-Geisser corrected in order to deal with heterogeneity in covariance. Error probability was predefined at $p < .05$ (two-tailed) and significance level was adjusted for multiple comparisons where appropriate.

Figure 1: different stimuli for the Simon task



Left rectangle stimuli, right eye-like stimuli. Each stimulus was presented 60 times in random order. During the first run only rectangle stimuli were presented, during the second only eye-like stimuli. Stimuli were either in blue or green in both conditions. Subjects were instructed to push a designated button for each color as fast as possible after stimuli had appeared on the computerscreen.

Results

Demographics

Patients had significantly fewer years of education (10.5 vs. 11.9 years, $t(61)=9.336$, $p<.001$) a fact generally inherent to the diagnosis of schizophrenia (). The patient group treated with antipsychotics had a significantly longer illness duration (27 vs. 13 month ($t(27.5)=2.7$, $p=.012$)). Mean values for the four PANSS factors were: positive symptoms: 11.6 (SD 6.9); negative symptoms: 17.7 (SD 8.2); general symp

toms: 27.6 (SD 12.3) and total PANSS score: 54 (SD 25). Mean dosage of antipsychotics was 315 (SD 139) CPZ-equivalents.

Simon task

Errors were few (less than 4%) in both groups without significant differences (all p-values>.15) and evenly distributed among conditions, thus all participants correctly followed the task instructions. As expected, schizophrenia patients had significantly longer reaction times (RT) than healthy controls in each subtask with all p-values<.005. (for all values see table 1 and figure 2)

The fixed-effect order of the experiment could cause statistical effects due to different amounts of fatigue in the different groups. Therefore we calculated a mixed -design ANOVA on the mean reaction times of the two conditions (rectangles, eyes) and group (SC, HC). As expected the factor group was significant ($F(1,61)=16.479$, $MSE=18686.3$, $p<.001$, $\eta p2 =.216$), but there was no effect of task ($F(1,61)=0.003$, $MSE=2296.5$, $p=.958$, $\eta p2<.001$) or an interaction ($F(1,61)=0.73$, $MSE=2296.5$, $p=.788$, $\eta p2 =.001$). The comparison between medicated and un-medicated patients revealed similar results, but now even the factor group ($F(1,31)=0.62$, $MSE=31206.3$, $p=.437$, $\eta p2 =.02$) did not reach significance (task: $F(1,31)=0.003$, $MSE=2237.2$, $p =.96$, $\eta p2<.001$; group by task: $F(1,31) = 0.823$, $MSE = 2237.2$, $p =.372$, $\eta p2 <.027$). Thus, the fixed order did not affect RT between groups in a different way.

We calculated the same mixed -design ANOVA on the number of errors of the two conditions (rectangles, eyes) and group (SC, HC). The main factors and the interaction were not significant: group ($F(1,61)=1.617$, $MSE=1303.1$, $p=208$, $\eta p2 =.026$); task ($F(1,61)=2.415$, $MSE=306.4$, $p=.125$, $\eta p2=.038$); group by task ($F(1,61)=0.13$, $MSE=306.4$, $p=.910$, $\eta p2 <.001$). The comparison between medicated and un-medicated patients revealed similar results: group ($F(1,31)=0.639$, $MSE=887.2$, $p=.430$, $\eta p2 =.02$); task: $F(1,31)=0.155$, $MSE=205.7$, $p =.696$, $\eta p2=.005$; group by task: $F(1,31) = 1. 251$, $MSE = 205.7$, $p =.272$, $\eta p2 <.039$). Thus, the fixed order did not affect error rates between groups in a different way. None of the groups did show signs of increased fatigue in the second part of the experiment (eye-condition).

First, we compared the two patient groups and performed a mixed-design ANOVA on the mean reaction times with gaze (congruent, neutral, incongruent) and task (rectangle, eyes) as within subject factor and group (SC_med, SC_unmed) as between subject factor. Results showed no main effects (task: $F(1,30)=0.003$, $MSE=6711.6$, $p=.960$, $\eta p2=.000$; gaze: $F(1.834, 55)=2.422$, $MSE=1706.5$, $p=.103$, $\eta p2=.075$; group, $F(1,30)=0.620$, $MSE=19359.3$, $p=.437$, $\eta p2=.02$) and no interactions (task by group: $F(1, 30)=0.823$, $MSE=6711.6$, $p =.372$, $\eta p=.027$; gaze by group: $F(1.834, 55)=0.001$, $MSE=1706.5$, $p=.998$, $\eta p2=.002$; gaze by task by group: $F(1.774, 53.2)=0.975$, $MSE=937.3$, $p=.975$, $\eta p2=.031$). We therefore pooled the data for all patients and compared these with the group of healthy controls.

Table 2: Reaction times

	Healthy controls		**Patients: all**		**Patients: medicated**		**Patients: unmedicated**	
	n = 30		n = 33		n = 23		n = 10	
Square	mean	SD	mean	SD	mean	SD	mean	SD
neutral	442	68	542	127	559	122	505	139
congruent	442	70	539	136	551	123	511	165
incongruent	450	70	558	148	567	146	534	159
Facilitation	0	26	3	95	8	32	-6	42
Interference	8	21	16	52	9	57	30	38
Eye								
neutral	445	65	541	123	545	109	531	158
congruent	433	70	540	122	546	112	526	148
incongruent	463	74	550	138	558	137	530	148
Facilitation	12	95	1	43	-1	51	6	23
Interference	18	101	9	52	13	60	-1	28
Simon effect								
Square	8	24	19	46	17	52	24	30
Eye	30	30	10	55	12	63	5	30

Reaction times in milliseconds for healthy controls vs. schizophrenic patients (left) and for medicated vs. unmedicated patients (right). Below Simon effect (incongruent condition minus congruent condition). RT: reaction times in milliseconds. For statistical details, see the result sections

The differences of the overall intra-individual RT and intra-individual standard deviation between the two patient groups were not significant for RT (SC_med: 554, SC_unmed: 538; t(31)=0.356, p=.724) and standard deviation (SC_med: 192, SC_unmed: 155; t(31)=1.124, p=.27). In addition, the coefficient of variance did not differ significantly (SC_med: 0.331, SC_unmed: 0.276; t(31)=1.527, p=.137).

We performed the same mixed-design ANOVA as for the two patient groups with healthy controls and all patients as between subject factor group. Results showed an effect of gaze, F(1.743, 106.3)=5.799, MSE=1867.6, p= 006, ηp2=.087, and group, F(1,61)=16.479, MSE=9343.1, p<.001, ηp2=.216, but there was no effect of task, F(1,61)=0.003, MSE=6890.2, p=.958, ηp2<.001 and no interaction (gaze by group, F(1.743,106.3)=0.096, MSE=1867.6.2, p=. 883, ηp2=.002, task by group, F(1,61)=0.073, MSE=6890.2, p=.778, ηp2=.001, or gaze by task by group F(1.563,95.3)=1.373, MSE=1867.6.2, p=.256, ηp2=.022.

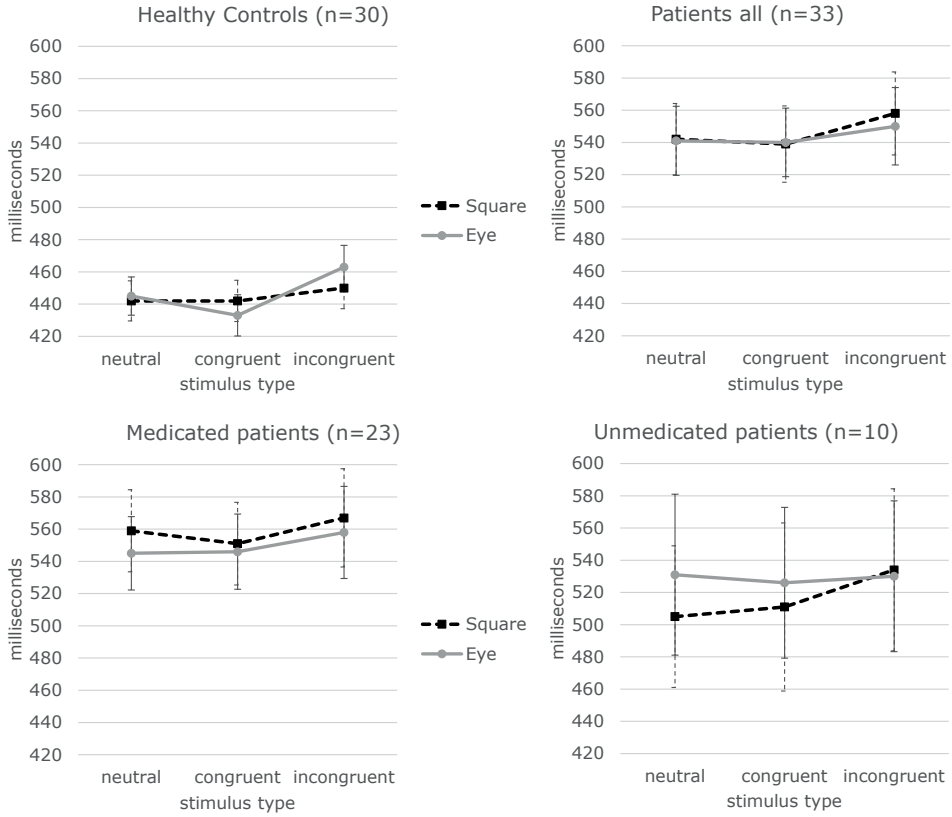
The differences of the overall intra-individual RT and intra-individual standard deviation between the two groups were significant for both RT (HC: 442, SC: 549; t(48.1)=4.29, p<.001) and standard deviation (HC: 102, SC: 180; t(46.2)=4.56, p<.001). In addition, the coefficient of variance was significantly higher in the patient group (HC: 0.225, SC: 0.313; t(55.78)=4.11, p<.001).

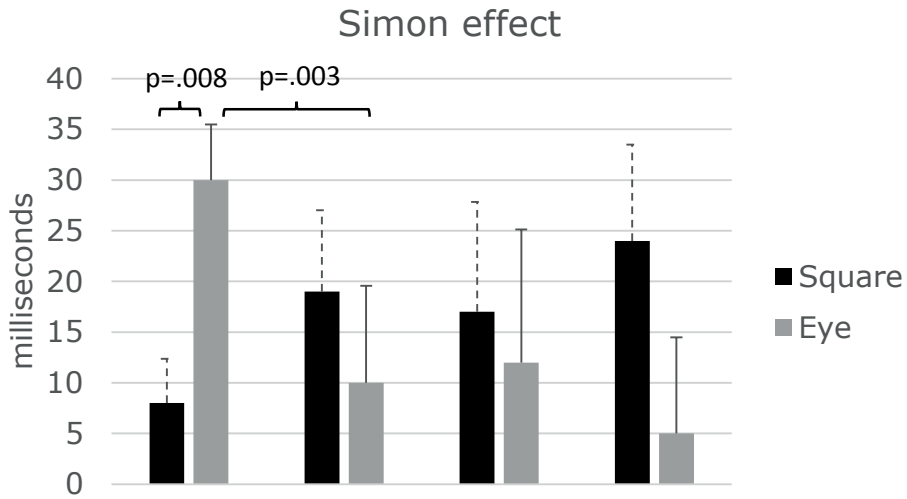
Simon effect

Although we found no significant interactions of gaze by group or gaze by task by group in the above analysis, it was possible that the neutral condition added noise and so we calculated an index of the Simon effect for both tasks (Congruent – Incongruent) for each subject. As for mean reaction times, we compared these for the two patient groups by entering these values into a mixed-design ANOVA with stimulus type (rectangles, eyes) as with within subject factor and group (SC_med, SC_unmed) as between subject factor. Again main effects and interaction were not significant (task: F(1,30)=0.854, MSE=2048.8, p=.363, ηp2=.028; group, F(1,30)=0.01, MSE=3592.0, p=.976, ηp2<.001; task by group: F(1, 30)=1.291, MSE=2048.8, p=.265, ηp2=.041). We therefore pooled the data for all patients and compared these with the group of healthy controls.

We performed the same mixed-design ANOVA as for the two patient groups with HC and all patients as between subject factor group. Results showed a significant interaction, F(1,61)=5.474, MSE=1321.9, p=.023, ηp2=.082, but there were no main effects (task, F(1,61)=0.951, MSE=1321.9, p=.333, ηp2=.015; group F(1,61)=0.279, MSE=1052.8, p=.599, ηp2=.005l). Post hoc t-test revealed that the healthy controls were more disrupted by the eye-like stimuli (mean difference 30 ms) than by the rectangle stimuli (mean difference 8 ms, Wilcoxon, p<.008), and patients' responses were more, but not significantly affected by rectangles (mean difference 19 ms) than by eyes (Mean difference 10 ms,

Figure 2: Reaction times for the different groups and Simon effect.





Reaction times (RT) in milliseconds with standard errors for healthy controls and all schizophrenic patients (above) and for medicated and unmedicated patients (middle). Below Simon effect (incongruent condition minus congruent condition). For statistical details, see the result sections.

n.s.). Furthermore, the Simon-effect differed significantly between the two groups in the eye-like condition (30 vs 10 ms, Kolgomorov-Smirnow, p<.003), but not in the rectangle condition (8 vs 17 ms, Kolgomorov-Smirnow n.s.). These effects remained significant after correction for multiple comparisons (p=.05/4=.0125).
To evaluate the effect of medication and psychopathology on the results, we performed correlation analysis between the calculated Simon effect for the two conditions, the four PANSS-factors and CPZ equivalents in the patient group. All correlations were non-significant (all p-values > 0.4). In addition we calculated the correlation between level of education and the Simon effect in the two conditions for the patient group, which were also non-significant in both the rectangle (r=-.19, p=.28) and in the eye-like (r=-.04, p=.82) condition.

We finally examined whether the observed Simon effect was driven by interference (mean RT of the incongruent minus the neutral condition) or facilitation (mean RT of the neutral minus the congruent condition) in comparison to the neutral condition. We performed a mixed-design ANOVA on the mean reaction times with gaze direction (interference, facilitation) and task (rectangle, eyes) as within subject factor and group (SC_med, SC_unmed) as between subject factor. None of the main effects or interactions reached significance (all p>.15). The same analysis with all patients with schizophrenia versus healthy controls showed a significant interaction between task and group ($F(1,61)=5.474$, MSE=661.0, p=.023, $\eta p2=.082$), but none of the other main effects or interactions was significance (all p>.33). Similar to the analysis of the Simon effect (see above) this interaction is driven by a significant difference of the reaction times between task conditions in the group of healthy controls (Wilcoxon, p<.008), while no difference was found in the group of patients (Wilcoxon, p=.567).

In conclusion, patients with schizophrenia had longer reaction times in all conditions, as expected. The mean difference between the congruent and incongruent condition (Simon-effect) was significantly greater in the eye-like condition for healthy controls in comparison to the rectangle condition and greater than the eye-like condition in patients with schizophrenia. Current psychopathology or treatment with antipsychotics as expressed in CPZ-equivalents did not influence the results. Although the reaction times between treated and untreated patients differed, these differences did not reach significance.

Discussion

The aim of our study was to examine the effect of social cues on automatic spatial coding in patients with schizophrenia compared to healthy controls. First, we confirmed our primary hypothesis. Patients with recent-onset schizophrenia had a significantly smaller Simon effect in the eye-like condition than healthy controls. Thus, it seems that these patients are less amenable to spatial coding by gaze cueing, which confirms our theoretical assumption of a weakened link between social and

"cold" cognition in schizophrenia. Our findings were not influenced by psychopathology or antipsychotic medication. We found no differences in performance between medicated and un-medicated patients, and no correlations between PANSS-scales, CPZ-equivalents and RT or the Simon effect in the total group of patients.

Secondly, we reproduced the results of Zorzi et al. (2003) in healthy control subjects. Although a small Simon effect could be detected in healthy controls for the rectangle condition, this effect was significantly bigger in the eye-like condition. However, for the raw RT we did not find an interaction between the two conditions (eye, square) and group. This is probably caused by the much higher intra-individual variability in the patient group, as shown by a significant higher standard deviation and coefficient of variance. The original Simon effect itself is described as the difference between RT for stimuli in lateralized presentation without a neutral condition. Similar to the Stroop task, the main focus of interest is on the difference between the two extreme conditions (congruent-incongruent). This theoretical focus justifies excluding the neutral condition from the main analysis.

The only study that examined the Simon-effect in patients with schizophrenia (Gastaldo, Umilta, Bianchin, & Prior, 2002) found a reduced Simon effect for patients. However, the group size in this study was relatively small and patients with predominantly negative symptoms and a longer duration of illness were included. The Simon effect was only present in the left, but not in the right hemifield. In our study, neither patients with schizophrenia nor the healthy controls had a Simon effect in the rectangle condition. However, it has to be taken into account that the design of our study differed from a typical Simon task because stimuli were presented bilaterally (see figure 1).

The neutral gaze direction gave us the opportunity to analyse possible interference or facilitation effects. Using a design with two different neutral conditions in a classical Simon task, Aisenberg and Henik (2010) found significant interference effects in both conditions, and in one of the two conditions a significant facilitation effect. Conversely, we found no effect of interference or facilitation in any of the conditions or groups. We suggest that this is the consequence of the more central presentation of stimuli in our study. The Simon effect of more than 50ms reported by Aisenberg and Henik (2010), was nearly twice as large than the Simon effect found in the eye-like condition in healthy controls of our study.

When the same stimuli as in our study were used to direct attention to a stimulus appearing in one of the hemifields (Akiyama et al., 2008b), healthy control subjects had a congruency effect evoked by eyes, rectangles and arrows, which directed attention to the hemifield in which the subsequent stimuli appeared. In contrast to our results, patients with schizophrenia had a nearly significant congruency effect for eyes, but no congruency effect for rectangles. The latter result was further corroborated by a control experiment, in which patients were explicitly advised to recognize the rectangles as eyes, but again no congruency effect was

detected[1].

Thus, it seems that patients are not prone to perceive rectangles as eye-like stimuli. This finding in patients conforms to the results of our study. However, there are differences between the examined patient groups. Their patient group comprised chronic patients who had more symptoms (PANSS total score of 82) and used higher doses of medication (12.8 haloperidol-mg equivalents which corresponds to 768 CPZ-equivalents) than the patients who participated in the present study. In contrast to the findings of Akiyama et al. (2008a), healthy subjects in our study could not use rectangles for spatial coding.

A similar experiment, but using photographs of human faces with gaze straight or directed to the left or right, found similar effects of gaze cueing on spatial attention in a group of 14 patients with recent onset schizophrenia (all treated with antipsychotic medication) as in healthy controls (Magnee et al., 2011). In contrast, a study using the inhibition of return paradigm has been shown, that the shift of spatial attention is impaired in patients with schizophrenia (Nestor et al., 2010). The effect of gaze cueing lasted longer in patients with schizophrenia than in normal controls, with a possibly reduced attention for new upcoming stimuli at other locations of the visual field.

However, these experiments differ in several aspects from ours. Firstly, gaze deviation preceded the appearance of the stimulus, on which subjects had to react, while in our task gaze was an inherent, but irrelevant stimulus property. Secondly, stimuli to which subjects had to respond had a spatial property by being displayed either in the left or right hemifield. Thirdly, response by itself had to be performed only by one hand and key (Akiyama et al., 2008b; Nestor et al., 2010), while in our task, the specific aspect was the lateralized motor response. Thus, while these previous experiments examined the influence of a cue on spatial attention (Akiyama et al., 2008b; Langdon et al., 2006; Magnee et al., 2011; Nestor et al., 2010), only our experiment examined the influence of spatial coding on stimulus-response conflict.

In the light of previous research we interpret the presented results as an impairment of patients with schizophrenia in the fast and automatic coding of gaze direction (Zorzi et al., 2003) when gaze is an implicit, non-relevant stimulus feature. In a more general sense, patients with schizophrenia are impaired in using social information as displayed by the eye-like stimuli to guide behaviour within specific (Akiyama et al., 2008b; Nestor et al., 2010), but not all (Langdon et al., 2006; Magnee et

[1] An anonymous reviewer suggested, that the difference between the two types of stimuli, squares vs. eyes, as non-social or social is somewhat blurred and that patients growing up with watching TV cartoons or reading comics are used seeing eyes represented by rectangles with coloured squares inside. However, this holds true for both, healthy controls and subjects, and the results of the here mentioned study suggest, that, especially patients with schizophrenia do not see eyes in the rectangle stimuli. Furthermore, it seems reasonable that both patients and controls grew up in a similar environment, suggesting that both are likewise familiar with comics and TV cartoons.

al., 2011) circumstances. This impairment seems not to be explained by a reduced ability of patients with schizophrenia to correctly recognize gaze not directed to them. They perform as well as healthy controls in gaze discrimination to the left or right (Franck et al., 1998; Kohler et al., 2008), but experience difficulties, when gaze is directed towards them (Franck et al., 2002). Similar results have been reported by Hooker and Park (2005), who found a specific deficit of gaze discrimination at a deviation of 30 degrees.

Altogether, the results from the different studies suggest that patients with schizophrenia are not generally impaired in the perception of gaze. However, the influence of gaze on cognitive processes such as attention or estimation of spatial distances seems to be smaller in patients, especially when gaze is an irrelevant stimulus property.

Several authors (Akiyama et al., 2008b; Tipper, 2010; Zorzi et al., 2003) suggested that an "eye-direction detector" (Baron-Cohen, 1994) is essential for the observed advantage found in the eye-like condition. Neuroimaging findings (Adams, Gordon, Baird, Ambady, & Kleck, 2003; Engell & Haxby, 2007) suggest multiple regions involved in gaze processing, including the amygdala for emotional aspects and the superior temporal sulcus for detection of gaze direction. Both are part of a greater network involved in social perception, and an FMRI study found differences in these two regions in patients with schizophrenia compared to healthy controls (Pinkham, Hopfinger, Ruparel, & Penn, 2008). It has therefore been hypothesized, that patients with schizophrenia have a deficit in superior temporal sulcus function. However, as mentioned in the introduction, cognitive control mechanisms are also crucially involved in the Simon task. Cognitive control describes the ability to detect and act according to the rules that are relevant for the task at hand and suppress irrelevant information. Cognitive models of psychosis posit that a deficit in this domain is linked to the generation of symptoms such as disorganization and negative symptoms (Smith, Barch, & Csernansky, 2009) and it has been hypothesized that one of the core deficits in schizophrenia lies in the domain of cognitive control (Braver, Barch, & Cohen, 1999; Chambon et al., 2008). In contrast, we found, that patients with schizophrenia were less influenced by the (irrelevant) direction of gaze than healthy controls, which contradicts the hypothesis of a lack of cognitive control in patients with schizophrenia. One explanation may be that the present task relies less on cognitive control processes than on spatial coding. Thus, we suggest a possible interaction between social cues and spatial coding because we observed specific impairments in the "social" Simon task, rather than general impairments of cognitive control.

There are several limitations to our study. Because of our primary focus on social cues, we did not implement a standard Simon task to control for independent effects of the task itself. Another limitation is the fixed order of non-social and social cues, which was needed to avoid carry-over effects (Zorzi et al., 2003). However, the decrease of the Simon effect in the patient group and the increase of the Simon effect in the group of

healthy controls from the first to the second session do not support a general learning effect. Furthermore, we found no signs of fatigue, as absolute RT in both groups did not differ between the two conditions. Another limitation is that we did not find a significant interaction between gaze direction, task and group when we included the neutral condition in the analysis. However, as the Simon effect relies on the difference between laterally presented stimuli, we suggest that spatial coding by gaze directed to the left or right resembles the original idea of the Simon task in a stricter sense. Our choice to examine only males is justified by the finding (Bayliss et al., 2005) that gaze cueing effects differ between female and male participants. However, this choice limits the generalization of our findings to the general population and all patients with schizophrenia.

In conclusion, we found that automatic spatial coding processes are differentially influenced by eye-like and geometrical stimuli in patients with schizophrenia and healthy controls. Patients are less prone to use directed gaze in their response selection. Thus, the present study supports earlier findings of impaired processing of schematic gaze-direction cues in schizophrenia. Crucially, we demonstrate that this deficit affects early attentional processes in schizophrenia.

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Chapter 8

Summary, discussion and conclusions

The aim of this thesis was to increase our understanding of the way emotion modulates cognition in recent onset schizophrenia patients (ROS). After developing a new task to measure the interaction between emotional expressions and sustained attention (**chapter 2**), we investigated whether this interaction is disturbed in recent onset schizophrenia (**chapter 3**). Next, we investigated the interaction between emotion and attention in recent onset schizophrenia by using the emotional Stroop task (**chapter 4**).

We reviewed the literature to see how methodological differences influence results when studying emotional memory modulation in schizophrenia (**chapter 5**). Using these findings we investigated if disturbances in emotional memory modulation are present in recent onset schizophrenia patients and whether these disturbances are distinguishable between short- and long-term visual and verbal memory (**chapter 6**). Finally, we investigated social cognition in recent onset schizophrenia (**chapter 7**).

The influence of emotion on attention

Although there is a growing body of literature demonstrating both the beneficial (Anderson, 2005; Ohman, Lundqvist, & Esteves, 2001; Phelps, Ling, & Carrasco, 2006) and the interfering (Vuilleumier & Brosch, 2009) effect of emotion on performance in attention tasks, only a few studies investigated the influence of emotional expression on sustained attention. We designed a novel task in which positive, negative and neutral facial expressions were used as task irrelevant cues in a Emotional Continuous Performance Task (E-CPT) to study the influence of negative and positive emotion on sustained attention. First we compared the intrinsic test properties of the E-CPT with those of a classic letter CPT (AX-CPT) and second we investigated the influence of emotional expressions on sustained attention. The results are described in **chapter 2**. Although accuracy was lower and reaction time (RT) was longer in the E-CPT compared to the AX-CPT, this was most likely due to using stimuli that were harder to discriminate within sets and did not change the intrinsic test properties. In our E-CPT we found differential effects of emotion on reaction time and accuracy; faces with positive and negative emotion improved reaction time for the subsequent probe faces in comparison to neutral faces. This could be a result of affective priming (Palermo & Rhodes, 2007) which means that seeing an emotional face causes the subsequent neutral probe face to be perceived as the same emotion and therefore also receiving enhanced processing (Palermo & Rhodes, 2007). This effect is generally considered to be brief (200-500ms (Chun & Potter, 1995)), but affective priming can be prolonged beyond 500ms in conditions of low attentional load (Vuilleumier & Huang, 2009), such as in our study. Holmes, Bradley, Kragh Nielsen, and Mogg (2009) used a visual-probe task with angry, happy and neutral facial expressions as cues and non-emotional icon as probes (arrows) to investigate investigated the temporal course of attentional biases for facial expressions in HC. In their task, a neutral and an emotional cue face were shown side-by-side followed by an arrow

at the location of either the emotional or the neutral face. Participants were required to indicate which way the arrow was pointing. Just like in our study Holmes et al. (2009) found faster RTs when the probes appeared at the location of the emotional cue faces compared to when the probes appeared at the location of the neutral faces. The authors concluded that this is in line with an attentional bias for emotional compared to neutral faces. Because they also used electrophysiological measurements they could demonstrate that the attentional orienting to emotional faces began earlier for negative than positive faces (Holmes et al., 2009).

In our study the effect of facial emotional expressions on accuracy was specific to negative emotion; accuracy decreased after negative, but not after positive or neutral cue faces. Since negative stimuli capture more attention than positive stimuli (Eastwood, Smilek, & Merikle, 2003), negative cue faces might interfere with the processing of subsequent probes by placing a heavier demand on attentional resources (Yiend, 2010), resulting in lower accuracy. This reallocation of resources could also explain better visual short-term performance for angry compared to neutral and positive faces, even when facial expressions are a task irrelevant stimulus property (Jackson, Wolf, Johnston, Raymond, & Linden, 2008). In our study, emotion effects on probe perception were only present at the short (500ms) inter-stimulus interval and not in the long (5000ms) inter-stimulus interval. This is in line with the study by Ciesiellski et al. (2010) who studied the temporal course of attention-emotion interactions and found that emotions impede accuracy more, when the time between the emotional distracter and the target stimulus is relatively short. This means that for negative faces there is a speed-accuracy trade off; they induce a mode of processing focused on reacting fast but not especially accurate, which is in line with evolutionary explanations for an emotion-attention interaction. From an evolutionary perspective it is useful to increase processing only after a signal that something important is about to happen when sustained attention gets less efficient due to fatigue effects. Positive stimuli however speed up processing, but without interfering with efficiency; they induce a mode of processing focusing less on speed and more on evaluation of the surrounding stimuli, as is predicted by Frederickson's (Fredrickson, 1998) broadening hypothesis.

Patients suffering from schizophrenia have impairments on several emotional domains. Many of them report anhedonia (Burbridge & Barch, 2007) and they are often impaired in maintaining emotional, especially positive, experience over longer periods of time (Kring & Caponigro, 2010). They have difficulties in using facial cues for social judgment (Marwick & Hall, 2008) and often show reduced facial expressions themselves (Mandal, Pandey, & Prasad, 1998). They also suffer from difficulties in processing emotional expressions of human faces (e.g. Kohler, Walker, Martin, Healey, & Moberg, 2009; Morris, Weickert, & Loughland, 2009) which is independent from a generalized impairment in face perception (Goghari, Macdonald, & Sponheim, 2010). Nevertheless, at the moment of exposure to emotional stimuli the valence ratings and physiological

reactions for SC do not differ compared to HC (Hempel et al., 2005; Herbener, Song, Khine, & Sweeney, 2008); the in-the-moment experience of emotion is intact.

We used the same E-CPT described in **chapter 2**, to perform a study that investigated possible differences in the way emotion modulates sustained attention in ROS patients compared to HC (**chapter 3**). We replicated the general cognitive deficit that is usually found in ROS (Fioravanti, Bianchi, & Cinti, 2012); overall patients were less accurate and slower than HC. We hypothesized that if in ROS facial emotion recognition was impaired, they would suffer from less interference from emotional faces than healthy controls. We found a negativity effect, i.e. reduced accuracy when cues displayed a negative facial expression compared to neutral and positive expressions, comparable to the results in **chapter 2**. This negativity effect was similar in ROS and HC. Park, Kim, Kim, Kim, and Lee (2011) used a different E-CPT and found that happy facial expressions disturbed performance compared to neutral and negative expressions but also found that the effect was the same in HC and SC. Thus, emotional modulation of sustained attention is preserved in ROS in both their and our study. These results could at least in part be explained by the fact that in SC the priming of facial emotion perception by negative emotions is still intact in SC (Hoschel & Irle, 2001), despite impairments in facial emotion perception (Kohler, Walker, Martin, Healey, & Moberg, 2010). This means that HC and SC judge a neutral facial expression as significantly more negative when it is preceded by a negative emotional facial expression compared to when it is preceded by a positive or neutral emotional facial expression (Hoschel & Irle, 2001) and subsequently, the neutral face also receives increased attentional resources.

A major difference between the studies in **chapter 2 and 3** and studies that explicitly investigate facial affect recognition is that in our study facial affect was task irrelevant and therefore had an implicit effect on performance. When facial affect recognition is sampled explicitly participants have to study a face, recognize the emotion, translate it into a word and provide that answer. Lower scores on these tasks could represent an impairment in recognizing the expression, but also an impairment in translating a correctly recognized emotion into the correct answer. If the latter is the case in ROS, then implicit effects of emotion could still be intact, as in our study, while they score lower on facial affect recognition tasks.

Several studies investigating emotional modulation of attention and the associated brain activation found differences in either the interaction between frontal and limbic brain regions (Dichter, Bellion, Casp, & Belger, 2010) or between prefrontal brain regions and the amygdala (Anticevic, Repovs, & Barch, 2012) despite intact task performance. Therefore it is possible that the brain networks our ROS patients use to get intact task performance are different from HC (Kring & Caponigro, 2010). Combs and Gouvier (2004) showed that in SC attention is significantly predictive of affect perception scores. They used a four factor model of

attention and found that the "Shift" factor had the highest predictive value followed by "Encode" and "Focus-Execute" factors while the "Sustain" factor had the least predictive value (Combs & Gouvier, 2004). This suggests that the influence of emotion on cognition not only differs between different cognitive domains (memory vs. attention vs. working memory), but also between different subdomains (selective attention vs sustained attention).

To investigate the influence of emotion on selective attention, we used an emotional variant of a Stroop task, one of the classic tasks to investigate selective attention. A different group of ROS performed a Stroop task with both color and emotional words and the results are described in **chapter 4**. Similar to the results described in **chapter 3**, overall reaction time in ROS was longer than in HC. In both ROS and HC incongruent color words caused interference and congruent color words caused facilitation compared to neutral words. However no group differences or interactions where found which is in line with the study by Chen et al. in ROS (Chen, Wong, Chen, & Au, 2001). Although an effect of emotion on reaction times was present (longer reaction times for negative compared to neutral and positive words) this effect was present in both the ROS and the HC. Our results are in line with previous studies that used an emotional Stroop task in more chronic schizophrenia patients (Demily et al., 2009; L. K. Phillips, Deldin, Voglmaier, & Rabbitt, 2005). The present study demonstrates intact modulation of selective attention despite a general reduction in speed of processing in ROS, and in the presence of intact word-color congruency modulation of selective attention, that is, an intact Stroop effect.

Taking **chapter 2, 3 and 4** together, we can conclude that sustained and selective attention are influenced by task irrelevant emotional stimulus content. Effects are present for ecological relevant, visual stimuli but also for abstract verbal stimuli. However effects are not congruent. For sustained attention emotion in general facilitates reaction times in healthy controls in the first study, but to a lesser extent in the second study. In contrast, negative emotional verbal stimuli increase reaction times in the Stroop task. Negative emotional stimuli decreases accuracy in sustained attention, but emotion has no less influence on accuracy in selective attention, except an increased error rate for positive words in patients with schizophrenia. In summary, effects of negative stimuli are stronger than that of positive stimuli. In general ROS are impaired in sustained and selective attention as revealed by longer RT and reduced accuracy in both task. The main finding from the two studies with patients is a preserved emotional modulation of selective and sustained attention in ROS.

A possible explanation for the intact emotion-attention interaction could be that early in the course of schizophrenia, the emotional deficits are less severe than the attentional deficits (Anticevic & Corlett, 2012). In more chronic schizophrenia the in-the-moment experience of emotion is intact (see above) but the ability to retain the emotional experience over time is diminished (Ursu et al., 2011). We hypothesize that the ability to

retain emotional experience over a prolonged period of time is still intact early in the course of the disease.

Emotional memory modulation

Studies on emotional memory modulation (EMM) in patients with schizophrenia (SC) reveale contradictory results. Therefore we reviewed the literature to explore to which extent these contradictory results are caused by methodological differences (**chapter 5**) before we investigated EMM in ROS (**chapter 6**). For the review described in **chapter 5** we identified 14 studies describing 22 tasks were EMM was compared between SC and HC. Average sample size for SC was 23.0, maximum 37 and for HC 21.9, maximum 37. We found that two-thirds of the tasks showed no differences in EMM between SC and HC. In the remaining 8 tasks, SC showed less enhancement for positive, negative or both kinds of emotional stimuli. The contradictory results can be explained in part by methodological differences. Disturbances in EMM were found more often when long-term memory was tested than when short-term memory was tested. The main difference between short- and long-term memory processes is consolidation. In HC memory consolidation after sleep is better for emotional than neutral stimuli (Payne & Kensinger, 2010) and SC have sleep dependent disturbances in memory consolidation (see Manoach & Stickgold, 2009 for review). Consolidation of emotional memory traces is modulated by the amygdala (Cahill et al., 1996; McGaugh, 2000), a structure repeatedly linked to (emotional) dysfunctions in patients with schizophrenia (Aleman & Kahn, 2005; M. L. Phillips, Drevets, Rauch, & Lane, 2003). Therefore, we hypothesized that the impairment in EMM is caused by a problem in the consolidation of emotional stimuli in memory. We also found reduced emotional memory modulation on implicit but not explicit tasks. We interpreted this finding as an impairment of SC in the automatic or unconscious use of emotional stimulus content to enhance memory (see also Ranganath, Minzenberg, & Ragland, 2008). This is in line with the theory by Danion and colleagues that in SC the self-initiation of encoding strategies is defective, but not the execution of encoding strategies (Danion, Huron, Vidailhet, & Berna, 2007). We found no evidence that an overall memory deficit or the mode-of-retrieval were related to EMM.

Our next question was whether impairments in EMM are present in ROS and if there are impairments, whether they are differently present in long or short-term memory and whether they are differently present in the verbal or visual domain. To answer this question, we designed the study described in **chapter 6**. We tested visual and verbal short-term (immediate recall) and long-term (after 24h recognition) memory. We compared memory for previously validated neutral, negative and positive verbal (Hermans & Dehouwer, 1994) and visual (Lang, Bradley, & Cuthbert, 2005) stimuli. Similar to the overall attentional deficit found in **chapter 3 and 4** overall memory performance for ROS was significantly below that of HC on all tasks. Visual short-term memory accuracy was

better for both negative and positive stimuli, while for visual long-term memory accuracy was only enhanced for negative stimuli. Verbal short-term memory was decreased for negative words only, while in verbal long-term memory there was no EMM. Despite these differences between the tasks in the way emotion modulated memory performance, EMM did not differ between ROS and HC on any of the tasks. Herbener et al. (Herbener, Rosen, Khine, & Sweeney, 2007) did find less enhancement for positive stimuli in SC compared to HC in visual LTM, however they examined chronic schizophrenia patients. We found differences in the increase of memory performance between STM and LTM in the two groups with respect to visual but not verbal stimuli. The increase in performance in HC was significantly bigger than in ROS. This supports the hypothesis, that in ROS the consolidation process is impaired. However, the impairment seems more prominent in the visual domain and is modulated in the same way by emotion in ROS as in HC. Previous studies reported differences in EMM between STM and LTM (Calev & Edelist, 1993; Hall, Harris, McKirdy, Johnstone, & Lawrie, 2007). Both studies demonstrated that EMM is similar in HC and SC for STM. For LTM reduced EMM in SC compared to HC was reported for positive stimuli in both studies, but for negative stimuli only by one (Hall et al., 2007). Both studies examined chronic patients and included fewer participants than our study. This suggests, that although ROS already have memory impairments, these impairments only interact later in the course of the disease. This is in line with our results for the emotional modulation of sustained attention described in **chapter 3 and 4**.

In the review described in **chapter 5**, we found evidence that deficits in emotional memory modulation in SC are related to consolidation and that SC have a deficit in unconsciously using emotional content to modulate memory. We followed up on the consolidation hypothesis in **chapter 6** by comparing performance on short- and long-term explicit memory tasks. Our task design however, did not allow us to include an implicit memory task. So the question remains whether there are differences in emotional memory modulation between implicit and explicit memory tasks, since SC have difficulty automatically or unconsciously initiating strategies to enhance memory (Ranganath et al., 2008). The tasks in **chapters 3 and 4** had no explicit instructions however to focus on emotion and in these tasks the effect of emotion on cognition was the same in ROS as in HC. We therefore hypothesize that implicit memory tasks would show the same results in ROS as our explicit memory tasks. Related to a difference between implicit and explicit memory tasks, is the distinction between a shallow versus a deep level of processing of the stimuli that have to be remembered. In HC emotional memory enhancements were greatest when words (Jay, Caldwell-Harris, & King, 2008) or pictures (Ritchey, LaBar, & Cabeza, 2011) were encoded under a shallow versus deep processing condition. Because we used explicit memory tasks, we might have induced deep processing, especially for words, which are remembered at a semantic level and not based on their

physical appearance. This could explain why there was no effect of emotion in the verbal long-term memory task. It is possible that if we had induced a shallower processing of the stimuli, emotional effect would have been stronger and more subtle differences in emotional memory modulation between HC and ROS would have come to light.

Social cognition

Finally, **chapter 7** describes a study in ROS that investigates a specific part of cognition that is closely related to emotion: social cognition. The term social cognition generally refers to the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others; weighing social situational factors in making inferences about other people's beliefs, emotions and intentions (Green & Leitman, 2008). Social cognition in general is more correlated with social functioning than (neuro)cognition in SC (Fett et al., 2011).

We used an adapted version of the Simon task developed by Zorzi, Mapelli, Rusconi, and Umilta (2003) to investigate the effect of social cues on automatic spatial coding in ROS compared to HC. In a typical Simon task participants are required to react to the color of a stimulus. Although the position of the stimulus is irrelevant for performing the task, responses are faster and more accurate when the position of the stimulus corresponds to the position of the response key. Response selection is affected by irrelevant spatial information. In the task developed by Zorzi et al. (2003), instead of spatial information, gaze direction is used to affect response selection. Participants are shown a schematic drawing of human eyes with gaze directed to or away (social cues) from where participants had to react to the color of the (Zorzi et al., 2003). We investigated whether the modulation of reaction times produced by stimulus (in)congruities differs between ROS and HC and whether this effect is the same for social cues (drawing of schematic eyes) as non-social cues (rectangle). As expected based on the previous chapters, ROS had longer overall reaction times than the HC. We found no difference in Simon effect between groups in the rectangle (non-social) condition. However in our study ROS had a significantly smaller Simon effect (less facilitation and less distraction) compared to HC in the social cue condition. This means that automatic spatial coding is modulated less by a social cue in ROS. This effect is not due to a general perceptual deficit, as effects for ROS and HC did not differ in the rectangle condition. Despite the fact that some studies found that SC profited more from gaze cues than HC (Langdon, Corner, McLaren, Coltheart, & Ward, 2006), our results are more in line with a previous study by Akiyama et al. (Akiyama et al., 2008) in chronic schizophrenia. These findings support our hypothesis that in ROS the interaction between cognition (spatial coding) and social cues is weakened. The only previous study examining the Simon effect in patients with schizophrenia (Gastaldo, Umilta, Bianchin, & Prior, 2002) reported a reduced Simon effect in SC in one hemifield. However, this study differs to ours in

so many aspects that both studies are difficult to compare.

In line with the studies in **chapter 3, 4 and 6**, there were no correlations between the Simon effect and psychopathology. According to Bliksted et al. "social cognitive deficits in first-episode schizophrenia come in two distinct versions where one is a complex, cognitive demanding form linked with IQ. The other version is related to simpler forms of social cognition and independent of IQ" (Bliksted, Fagerlund, Weed, Frith, & Videbech, 2014). Our gaze cueing deficits seem to be more related to the latter category.

In the social cognition task described in **chapter 7** we used non-emotional social cues (the eyes were not embedded in faces with angry or happy expression) and we found a less modulation of attention in ROS. In **chapters 4 and 6** we used emotional stimuli (words and pictures), which held no social information and we found no difference in modulation of attention or memory in ROS. The emotional CPT task described in **chapter 3** was designed to investigate the influence of emotion on sustained attention and we used faces because they are a strong inducer of emotions and we found no difference in the way emotion modulated attention in ROS. Emotional face processing however is also considered part of social cognition (Green et al., 2008). So even if there already are deficits in social cognition in ROS, not all domains of social cognition are disturbed in this phase of the illness.

In **chapter 5** we argued that different and sometimes contradictory results in the literature on emotional memory modulation in SC were due to methodological differences. Of course, this is also true when comparing or integrating the results from the different chapters in this thesis. There are methodological differences because we wanted to examine the question "are there differences in emotion cognition interaction between ROS and HC?" from different perspectives. We investigated the way different aspects of emotion (positive, negative or social; elicited by pictures, faces or words) influenced performance on different cognitive domains. On the other hand, the studies described in **chapters 3, 4, 6 and 7** all included fairly large and homogeneous groups of participants compared to other studies investigating emotion-cognition interaction in schizophrenia; all participants were male and were between 17 and 35 years of age. Furthermore, all patients received a diagnosis of recent onset schizophrenia and used no or only one antipsychotic. We therefore hypothesize that, in the first clinical phase of schizophrenia in male patients, the way emotion in general influences various domains of (neuro)cognition is intact. Cognitive resources appear to linger at the emotional stimuli, speeding up their processing en keeping them stronger in (short-term) memory while making the processing of the subsequent neutral stimulus less efficient. The question remains however whether there are emotion cognition interaction deficits in more chronic schizophrenia. And if there are emotion cognition interaction deficits, why do they arise later in the course of the disease? When answering these questions, it will be important for future researchers to take into account that emotional modulation of cognition

not only depends on the type of emotional stimulus, but also on the cognitive domain that is tested. Therefore it is possible that different deficits in the interaction between subdomains of emotion and cognition occur at different time-points in the disease.

Limitations

Because some studies suggest that in schizophrenia age of onset and gender (van der Werf, Kohler, Verkaaik, Verhey, & van Os, 2012) influence cognitive impairments, we decided to include only male participants between the age of 17 and 35 years. Another reason to only include ROS was to control for effects of chronic medication use and effects caused by a long illness duration such as social under stimulation or chronic institutionalization (Nemoto, Niimura, Ryu, Sakuma, & Mizuno, 2014). This means that our results are not generalizable to chronic or older SC, but more importantly, they are not generalizable to female ROS. Although our sample sizes were relatively large for studies measuring emotion cognition interactions in schizophrenia, they were not large enough the compare subgroups of patients based on type of antipsychotic medication, ethnicity or whether they were admitted or treated ambulatory; all factors that could possibly influence the interaction between emotion and cognition.

Implications for Future Research

Our results raise some interesting questions that could be addressed in future research. First of all, our research shows that emotion cognition interactions are not disturbed in recent onset schizophrenia, while several others have demonstrated deficits in emotion cognition interaction in chronic schizophrenia. Longitudinal follow-up studies could give insight into when in the course of the disease these deficits arise and possibly into the processes that ensure that these deficits are not present from the onset of the disease. Another question that remains is whether our findings are specific to male ROS or whether they are generalizable to female ROS also.

Day to day functioning in SC is determined more by cognitive difficulties than by positive symptoms while the current antipsychotic medications mainly reduce psychotic symptoms and do not (yet) address the cognitive problems (Green & Nuechterlein, 2004; Lepage, Bodnar, & Bowie, 2014). In addition, it is also increasingly clear that cognitive behavioral therapy (CBT) is effective against some positive symptoms (Grant, Huh, Perivoliotis, Stolar, & Beck, 2012), while CBT is less effective when there are cognitive impairments. Therefore, there is increasing attention to non-pharmacological strategies to address cognitive impairments, such as cognitive remediation therapy (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Based on our results, more salient stimuli could be used in CBT and metacognitive training for ROS and perhaps even in patients in the prodromal phase of schizophrenia. Future research could then investigate if this makes these therapies more effective.

Another question that we did not address, is whether the interac-

tion between emotion and social cognition is disturbed in ROS. An elegant way to test this, is described in the study by Pecchinenda, Pes, Ferlazzo, and Zoccolotti (2008). In this study, HC reacted to words that were presented at the congruent or incongruent side of the computer screen from where emotional faces looked at. They found that only negative facial expressions enhanced the attentional shifts due to eye-gaze direction and only when participants had to react to the emotional content of the words. Comparing performance between ROS and HC on a similar task could tell us more about possible deficits in the interaction between emotion and social cognition in the early course of schizophrenia.

To conclude

The current thesis describes a number of important findings on the interaction between emotion and cognition in recent onset schizophrenia patients. In healthy controls a general effect of emotional expressions on sustained attention is that it improves reaction time while accuracy decreased after negative, but not after positive emotional expressions. Although ROS have a general attentional deficit, the effect of facial expressions on sustained attention is the same as in healthy controls. Furthermore, despite a general selective attention deficit, the emotional Stroop effect is not statistically different between ROS and HC. The literature on emotional memory modulation in SC shows contradictory results with two-thirds of the tasks finding no difference between SC and HC, this can be explained in part by methodological differences. Nevertheless, impaired emotional modulation of memory consolidation and a deficit in unconsciously using emotional content to modulate memory could underlie deficits in emotional memory modulation. In ROS emotional modulation is preserved, both in short and long term memory and for both verbal and visual memory. Social cognition, in the form of gaze cueing, however, is already disturbed in the early phase of schizophrenia.

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Chapter 9

Nederlandse samenvatting

Schizofrenie is een ernstige psychiatrische ziekte die wordt gekenmerkt door cognitieve problemen, psychotische symptomen (wanen, hallucinaties en desorganisatie) en emotionele gebreken. De cognitieve problemen en emotionele gebreken zijn beperkende factoren voor het dagelijks functioneren van patiënten met schizofrenie, meer nog dan de psychotische symptomen. Uit eerdere onderzoeken blijkt dat patiënten met schizofrenie problemen kunnen hebben op meerdere cognitieve domeinen: geheugen, werkgeheugen, executieve functies (de hogere controle functies van de hersenen) en aandacht. Daarnaast treden deze gebreken in mindere mate ook op bij niet aangedane familieleden van patiënten, wat bewijs is voor een genetische component bij de cognitieve problemen en het aannemelijker maakt dat de cognitieve problemen niet alleen een gevolg zijn van psychotische symptomen. Onder de emotionele gebreken bij patiënten met schizofrenie vallen verminderde gelaatsuitdrukkingen, problemen met het classificeren van emotionele gezichtsuitdrukkingen van anderen en een verminderd vermogen om zich te verheugen op toekomstige gebeurtenissen. De gevoelens en fysiologische reacties die emotionele stimuli oproepen bij patiënten met schizofrenie zijn echter wel hetzelfde als bij gezonde proefpersonen.

Van gezonde proefpersonen is bekend dat emotie invloed kan hebben op cognitieve functies; emotionele gezichten trekken meer aandacht dan neutrale gezichten en positieve of negatieve plaatjes worden beter onthouden dan neutrale plaatjes. Of deze wisselwerking bij patiënten met schizofrenie ook verstoord is, is minder duidelijk. Van gezonde proefpersonen is ook bekend dat vooral cognitieve functies afhankelijk zijn van leeftijd en geslacht. Daarnaast veranderen sommige cognitieve problemen en emotionele gebreken gedurende het beloop van de ziekte bij patiënten met schizofrenie en zouden ze beïnvloed kunnen worden door langdurig medicatiegebruik. Het doel van het onderzoek dat beschreven wordt in dit proefschrift is om meer duidelijkheid te krijgen over mogelijke verstoringen in de wisselwerking tussen emotie en cognitie bij patiënten met recent ontstane schizofrenie.

In **hoofdstuk 2** wordt onderzocht hoe emotionele gezichtsuitdrukkingen volgehouden aandacht beïnvloeden. Hierbij werd gebruikt gemaakt van een nieuwe door ons ontwikkelde taak. De ene helft van de deelnemers kreeg een serie gezichten te zien en moesten steeds reageren wanneer ze een bepaald vrouwengezicht ("probe") zag, maar alleen als het gezicht daarvoor ("cue") een mannengezicht was. De andere helft van de deelnemers deed dezelfde taak maar dan was de probe een bepaald mannengezicht en de cue een vrouwengezicht. Gekeken werd of de reactietijd en de accuraatheid veranderden als de "cue"-gezichten een positieve of negatieve gezichtsuitdrukking hadden in plaats van een neutrale gezichtsuitdrukking. Alleen gezonde studenten namen deel aan het onderzoek en het bleek dat de accuraatheid daalde na negatieve, maar niet na positieve gezichten en dat de reactietijd korter werd na zowel negatieve als positieve gezichten. Beide effecten waren alleen aanwezig als de tijd tussen de "cue" en "probe" gezichten kort (500ms) en niet lang

(5000ms) was en het effect werd versterkt door vermoeidheid. Dit is wel in lijn met evolutionaire verklaringen voor de wisselwerking tussen aandacht en emotie. Wanneer de aandacht dreigt te verslappen door vermoeidheid, kan een positieve of negatieve gezichtsuitdrukking een signaal zijn om even extra op te letten, omdat het waarschijnlijk is dat er dan iets belangrijks zal gaan gebeuren.

Het onderzoek dat beschreven staat in **hoofdstuk 3** gebruikt de taak uit **hoofdstuk 2** om de wisselwerking tussen aandacht en emotionele gezichtsuitdrukkingen te onderzoeken bij mannelijke patiënten met recent ontstane schizofrenie. Onze hypothese was dat als patiënten met recent ontstane schizofrenie moeite hebben om gezichtsuitdrukkingen te classificeren, de invloed van emotionele gezichtsuitdrukkingen op volgehouden aandacht bij hen verminderd zou zijn. Uit het onderzoek bleek echter dat, ondanks dat patiënten over het algemeen meer fouten maakten en langzamer reageerden dan gezonde proefpersonen, het effect van emotie op volgehouden aandacht in beide groepen hetzelfde was. De wisselwerking tussen emotionele gezichtsuitdrukkingen en volgehouden aandacht is dus niet verstoord bij patiënten met recent ontstane schizofrenie. Een mogelijke verklaring hiervoor is dat patiënten wel moeite hebben gezichten te classificeren, maar dat hun impliciete emotie en fysiologische reacties op emotionele gezichten nog wel intact zijn en ze dus volgehouden aandacht nog kunnen beïnvloeden.

Problemen met de selectieve aandacht zijn regelmatig beschreven bij patiënten met schizofrenie, ook in het vroege beloop van de ziekte. Vaak wordt de selectieve aandacht onderzocht met de Stroop taak. In de Stroop taak moeten deelnemers op namen van kleuren reageren, waarbij deze namen in verschillende kleuren afgebeeld zijn. Het Stroop effect houdt in dat het reageren sneller gaat wanneer de naam en de kleur overeenkomen (dus bijvoorbeeld GROEN geschreven in groen) en langzamer wanneer ze niet overeenkomen (dus bijvoorbeeld GEEL geschreven in rood). **Hoofdstuk 4** beschrijft een onderzoek waarbij deelnemers aan de emotionele Stroop taak niet alleen op de namen van kleuren moeten reageren maar ook op andere positieve, negatieve en neutrale woorden die in verschillende kleuren zijn afgebeeld. In het algemeen reageerden patienten trager dan gezonde proefpersonen. Er was een effect van emotie: reactietijden waren langer voor negatieve dan voor neutrale en positieve woorden, dit gold echter zowel voor de gezonde proefpersonen als voor de patiënten met recent ontstane schizofrenie. De resultaten wijzen er dus wederom op dat de wisselwerking tussen emotie en selectieve aandacht niet verstoord is bij patiënten met recent ontstane schizofrenie.

Om te zien of de verschillende uitkomsten die worden gerapporteerd in de literatuur over de manier waarop emotie het geheugen beïnvloedt bij patiënten met schizofrenie veroorzaakt worden door verschillen in de opzet van de onderzoeken deden we een literatuuronderzoek. De uitkomsten worden beschreven in **hoofdstuk 5**. De belangrijkste bevindingen waren dat twee-derde van de onderzoeken rapporteerde dat er geen verschil was tussen patiënten en gezonde proefpersonen in de

manier waarop emotie het geheugen beïnvloedt. In de studies die wel verschil vinden valt op dat er vaker verschillen worden gevonden wanneer het langetermijngeheugen wordt onderzocht dan wanneer het kortetermijngeheugen wordt onderzocht. Dit wijst op een mogelijk verminderde invloed van emotie op het consolidatieproces bij patiënten met schizofrenie. Verder vonden we in de literatuur vaker vermindering van de invloed van emotie op het geheugen bij patiënten wanneer er impliciete ("onaangekondigde") geheugentaken werden gedaan, dan wanneer er expliciete ("aangekondigde") geheugentaken werden gedaan. Dit past bij eerder onderzoek wat er op wijst dat patiënten met schizofrenie wel coderingsstrategieën kunnen gebruiken om hun geheugen te optimaliseren, maar dit niet automatisch doen.

In **hoofdstuk 6** wordt het onderzoek beschreven naar de wisselwerking tussen emotie en geheugen bij mannelijke patiënten met recent ontstane schizofrenie. Patiënten en gezonde proefpersonen deden korte- en langetermijngeheugentaken met neutrale, positieve en negatieve woorden en foto's. Gebaseerd op de resultaten van het literatuuronderzoek uit **hoofdstuk 5**, was onze verwachting dat eventuele problemen met de wisselwerking tussen emotie en geheugen vooral te zien zouden zijn bij de lange-termijn geheugentaken. Het geheugen in het algemeen bleek bij patiënten met recent ontstane schizofrenie slechter dan bij gezonde proefpersonen, wat in lijn is met eerder onderzoek. Daarnaast bleek in ons onderzoek dat de manier waar emotie het geheugen beïnvloedde afhing van het feit of er woorden of foto's werden gebruikt en of het lange- of kortetermijngeheugen werd getest. Voor iedere test gold echter dat de invloed van emotie op geheugen hetzelfde was bij patiënten als bij gezonde proefpersonen.

De term sociale cognitie verwijst naar de mentale processen die betrekking hebben op sociale interacties: het waarnemen en interpreteren van het gedrag en de lichaamstaal van anderen en daarop reageren en het afwegen van sociale situaties. Sociale cognitie is verwant aan (neuro)cognitie en aan emotieverwerking. **Hoofdstuk 7** beschrijft een onderzoek naar veranderingen in de invloed van blikrichting (een sociaal signaal) op responseselectie gemeten met een variant op de klassieke Simon taak. In een klassieke Simon taak moeten deelnemers op de kleur van een stimulus reageren. Hoewel de positie van de stimulus irrelevant is voor het uitvoeren van de taak, zijn reacties sneller en nauwkeuriger als de positie van de stimulus overeenkomt met de positie van de knop die past bij de kleur waarop ze moeten reageren. In onze taak wordt responseselectie niet beïnvloed door de positie van de stimulus maar door een illusie van blikrichting. Deelnemers zagen twee rechthoeken met daarin een vierkantje (geen sociaal signaal) of ze zagen twee ovalen met daarin een gekleurd rondje (een schematische tekening van ogen die naar voren, links of rechts konden kijken, dus wel een sociaal signaal) en moesten reageren op de kleur van de binnenste vormen. Reactiesnelheden van patiënten waren over het algemeen langzamer dan van gezonde proefpersonen. Het Simon effect was hetzelfde bij gezonde proefpersonen als

bij patiënten bij de rechthoekige figuren. Wanneer echter gebruik werd gemaakt van de op ogen lijkende figuren, was het effect van blikrichting op reactiesnelheid bij patiënten kleiner dan bij gezonde proefpersonen. Dit betekent dus dat bij mannelijke patiënten met recent ontstane schizofrenie de responseselectie minder door een sociaal signaal wordt beïnvloed dan bij gezonde proefpersonen.

In **hoofdstuk 8** worden de verschillende hoofdstukken samengevat en wordt geprobeerd de resultaten met elkaar te integreren. Hieruit volgt dat voor mannelijke patiënten met recent ontstane schizofrenie geldt dat, ondanks een verminderde aandachtfunctie, zowel de wisselwerking tussen emotionele gezichtsuitdrukkingen en volgehouden aandacht als de wisselwerking tussen emotionele woorden en selectieve aandacht nog intact is. Verbale en visuele emotionele stimuli beïnvloeden het korte- en langetermijngeheugen op een verschillende manier, maar de manier waarop dit gebeurt is in alle gevallen niet verstoord bij patienten met recent ontstane schizofrenie. Toch is bij deze groep patiënten de interactie tussen cognitie en sociale informatie, zoals blikrichting, wel verstoord. Metacognitieve training is een behandelvorm waarbij patiënten met een neiging tot psychotische klachten bewust worden gemaakt van veelvoorkomende denkfouten die tot psychotische klachten kunnen leiden. Toekomstige studies zouden kunnen onderzoek of patiënten met recent ontstane schizofrenie meer baat hebben bij lesmateriaal met een sterke emotionele lading als ze behandeld worden met (meta)cognitieve therapie. Daarnaast dient de wisselwerking tussen emotie en sociale cognitie verder onderzocht te worden in deze patiëntengroep.

Chapter 10

Dankwoord

"Personally I'm always ready to learn,
although I do not always like being taught."
(sir Winston Churchill, 1874-1965)

"Have no fear of perfection - you'll never reach it."
(Salvador Dalí, 1904-1989)

Dankwoord

Bij het schrijven van mijn dankwoord begon ik in mijn geheugen te graven om te bedenken welke mensen tijdens mijn onderzoeksperiode een positieve herinnering bij mij achtergelaten hebben, vaak door de aandacht en de steun die ze mij gaven. Hoewel ik hoop dat ik iedereen, die me op welke manier dan ook geholpen heeft, al persoonlijk heb bedankt, zijn er een aantal mensen die ik ook hier speciaal wil noemen.

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Rotterdam, oktober 2014

Chapter 11

Curriculum Vitae
List of Publications
PhD Portfolio

Curriculum Vitae

Sieds Dieleman was born on May 19th 1979 in Zwijndrecht, the Netherlands. He went to high school at the Develstein College in Zwijndrecht, where he obtained his VWO-diploma in 1997.

From 1997 to 2002 he studied medicine at the Erasmus University Rotterdam, where he received his masters' degree (doctoraal) in 2002. After graduating for his medical degree in 2005, he worked as a psychiatry resident for Parnassia in The Hague. From 2005 to 2012 he received his training as a psychiatrist at the department of psychiatry at the Erasmus Medical Centre in Rotterdam and RIAGG Rijnmond in Rotterdam. On September 1th 2012, he was registered as a psychiatrist.

During his training as a psychiatrist, he started as a PhD candidate in 2007 at the department of psychiatry at the Erasmus Medical Centre. For this project he received an OOG-grant (Opleiding Onderzoekers GGZ) from ZonMW, the Netherlands Organization for Health Research and Development.

After working as a psychiatrist at Delta Center for Mental Health Care in Rotterdam from 2012 to 2014, he now works at Bavo-Europoort Psychiatric Institute, Rotterdam.

He lives together with Nicole Meijer, they have three children; Wouter, Nora and Lotte.

International publications

- Dieleman, S., & Röder, C. H. (2013). Emotional memory modulation in schizophrenia: an overview. Acta Psychiatrica Scandinavica, 127(3), 183-194. doi: 10.1111/acps.12047
- Röder, C. H., Dieleman, S., Mohr, H., Sterrenburg, A., van Beveren, N., & Linden, D. E. J. (2014). Impairment of gaze-directed spatial coding in recent-onset schizophrenia. The Quarterly Journal of Experimental Psychology, 1-35. doi: 10.1080/17470218.2014.938665
- Röder, C. H., Dieleman, S., van der Veen, F. M., & Linden, D. (2013). Systematic review of the influence of antipsychotics on the blood oxygenation level-dependent signal of functional magnetic resonance imaging. Current Medicinal Chemistry, 20(3), 448-461.

Submitted papers

- Dieleman, S., van der Veen, F. M., van Beveren, N., & Röder, C. H. Preserved emotional memory modulation in first episode psychosis. submitted.

Other publications

- Nimwegen, L. J. M., Brand van den, R. P., Ju, M. R., & Dieleman, S. (2008). Leidraad psychiatrie (M. W. Hengeveld Ed.). Houten, the Netherlands: Bohn Stafleu van Loghum.

PhD Portfolio: Summary of PhD training and teaching

Name PhD student: S. Dieleman	PhD period: 2007-2014	
Erasmus MC Department: Psychiatry	Promotor(s): M.W. Hengeveld	
Research School:	Supervisor: C.H. Röder/F. v.d. Veen	
1. PhD training	***Year***	***Workload (ECTS)***
General courses		
Statistics	2010	2 ECTS
Biomedical English Writing and Communication	2011	4 ECTS
Research Integrity	2011	2 ECTS
Presentation skills	2012	.5 ECTS
Specific courses (e.g. Research school, Medical Training)		
Cognitive and Affective Neuroscience, dept. Psychology EUR	2010	5 ECTS
Course Biological Psychopathology, dept. Psychology EUR	2011	5 ECTS
Seminars and workshops		
Introductory Course on Statistics & Survival Analysis	2010	.5 ECTS
Symposium Neuroimaging, Genetics, and Endophenotypes	2010	.5 ECTS
Presentations		
Poster presentation VJC NVVP	2007	1 ECTS
Poster presentation SIRS conference Venice	2008	1 ECTS
Poster presentation IEPA conference Amsterdam	2010	1 ECTS
Poster presentation SIRS conference Florance	2012	1 ECTS
Research presentation Erasmus MC, dept. Psychiatry	2012	.5 ECTS
Research presentation Delta Psychiatrisch Centrum	2013	.5 ECTS
(Inter)national conferences		
SIRS conference Venice	2008	1 ECTS
SIRS conference Florence	2010	1 ECTS
IEPA conference Amsterdam	2010	1 ECTS
SIRS conference Florence	2012	1 ECTS
Other		
Attending seminar series Department of Psychiatry Erasmus MC 1h/week	2007-2011	2 ECTS
Attending Schizophrenia Workgroup journal club 1h/week	2009-2012	1 ECTS
2. Teaching	***Year***	***Workload (ECTS)***
Lecturing		
Masters Course for Nurse Practitioners	12-11-2010	3 ECTS
Onderwijs ICK co-assistenten	2011	3 ECTS
Onderwijs 3e jaars studenten	2011	1 ECTS
Onderwijs opleiding GZ-psycholoog	2012/13/14	3 ECTS
Supervising practicals and excursions, Tutoring		
2e jaars KOW	2011	2 ECTS
Supervising Master's theses		
Master's theses C. Simons	2010	4 ECTS
Other		
Participating in designing "VO psychiatrisch onderzoek"	2010/2011	1 ECTS