When Emotion Meets Cognition

Emotion-cognition interaction in healthy controls and patients with schizophrenia

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Colofon
When Emotion Meets Cognition

Thesis, Erasmus Universiteit, Rotterdam, The Netherlands

ISBN/EAN: 978-90-5335-750-7

Cover: Nikki Vermeulen, Ridderprint BV, Ridderkerk, the Netherlands
Druk: Ridderprint BV, Ridderkerk

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When Emotion Meets Cognition.

Emotion-cognition interaction in healthy controls and patients with schizophrenia

Als emotie ontmoet met cognitie

Emotie-cognitie interactie in gezonde controles en patienten met schizofrenie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

vrijdag 15 November 2013, om 13.30 uur

Christian Heinrich Röder
geboren te Limburg an der Lahn

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Habe nun ach! ....

J.W.Goethe, Faust, 1. Teil

Noch der armseligste Mensch, ist fähig, die Schwächen des bedeutensten, noch der dümmste, die Fehler des klügsten zu erkennen.

T. W. Adorno, Minima Moralia

If the human brain were so simple that we could understand it, we would be so simple that we couldn’t.

Emerson M. Pugh, The Biological Origin of Human Values

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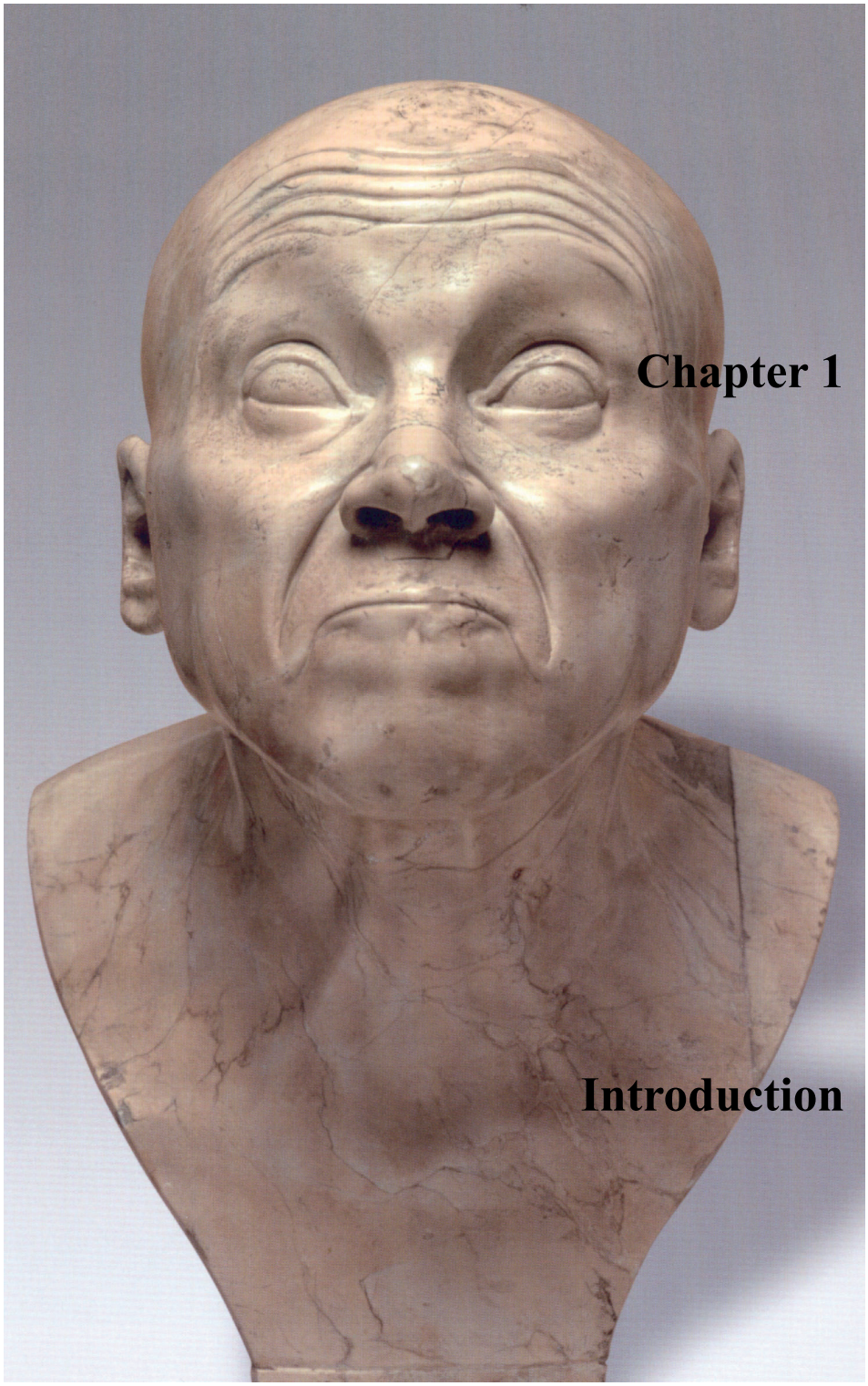

Chapter 1

Introduction

Introduction

Human mental processes are a continuous interplay between sensations derived from the outer world, internal states such as beliefs and intentions, conscious and unconscious memories from earlier experiences and affective evaluation of all these parts. During everyday life, no one wonders about which of these processes would be called cognitive and which emotional, because for most individuals mental processes are experienced as direct and unified. Only reflecting on mental processes by the individual or an external observer leads to a distinction between the processes mentioned above. Almost everyone would say that there is one basic distinction: cognitive versus emotional processes. As the soul, psyche, was mainly the domain of philosophical interest until the midst of the 19th century, it is not surprising that ancient Greek philosophy already tried to develop concepts that explain the different functions of the psyche. At that time, terms as cognition and emotion were not used. Plato in 'Politeia' suggested that the soul is divided in three parts: reason, spirit and appetite. While reason aims to reach wisdom and is characterized by its ability to search for what is good for the soul, spirit aims to gather honour and appetite aims to receive satisfaction for bodily needs. As Plato wanted to develop a theory of the ideal state, the consequence is that reason has to dominate spirit and appetite in order to reach virtue [1]. Based on this model Plato explained how "intra-psychic" conflicts could occur when for example appetite seeks satisfaction but reason defends the virtue of wisdom.

The great opponent of Plato, Aristotle, proposed another model, which attracted modern theories of the psychology of emotion more often [2]. Aristotle proposed that the soul is not divided, but the soul inherits different capacities: reasoning, appetency and emotion. In agreement with Plato, Aristotle demands that reasoning dominates appetency and emotion. But in contrast to Plato, Aristotle states that appetency and emotion do not have to be eliminated to reach virtue. Furthermore, Aristotle argues that all human operations have an emotional value for the executor and that in addition emotions cause operations [3]. As operations are the consequence of reasoning, reasoning and emotions are strongly connected with each other.

A similar conceptualization was made early in the beginning of modern psychology. One of their founders, Wilhelm Wundt, states in his textbook 'Grundzüge der Physiologischen Psychologie' that "Vorstellungen", which can be translated as cognitive functions, are always accompanied by "Gemüthsvorgängen", which can be translated as emotions [4]. More importantly, he states that "accompany" does not only mean a coexistence of separable conditions but that both are part of a unitary system[1]. However, psychology ignored this idea for a long time.

1 The original quotation is: "Sowohl die einzelnen Vorstellungen wie der Wechsel derselben, ihre Associationen und Apperceptionen sind, wie uns die vorangegangenen Capitel gezeigt haben, überall von Gemüthsvorgängen begleitet, und dieses Begleiten bedeutet nirgends eine bloße regelmäßige Coexistenz an sich trennbarer Zustände, sondern einen einheitlichen Zusammenhang

When talking about cognition and emotion, both terms seem to represent well-defined entities, but actually both are metaphors for observations of human behaviour and can be examined from various perspectives such as philosophy, psychology and biology, and even computer-science.
For cognition, to a much greater extent than for emotion, there is a common sense, what someone means when speaking about cognitive functions. There is little doubt that attention, memory, perception etc. can be well defined, and that these functions can not only be observed in humans but also, to a lesser extent, in animals. Although cognitive processes manifest themselves in behaviour, they are primarily seen as purely psychological processes, which of course have a biological basis in cerebral processes.

Cognitive psychology and neuroscience

For a long time cognitive psychology has used computational models mainly to explain cognitive processes by decomposing them in sub-processes. For example: a memory task comprises several mental processes such as attention; encoding; consolidation; rehearsal; reproduction; and maybe even more. All of these are necessary to perform a task examining 'memory'. The typical models provided by cognitive psychologists propose a serial processing of the individual sub-processes, which can be rebuild in a computer-model [5]. The sub-processes are computed by hypothesized modules inherent in a system, which in the end can be a human subject but also a machine (computer). Although much of the observation of human behaviour can be explained by the computational approach and can be simulated by computer-programs, several problems arise. First of all, processes in the brain are not serially, but parallel, so the model may explain and predict behaviour correctly, but does not correspond sufficiently to underlying biological and neurophysiological mechanisms. Secondly, the model of modules suggests them as biological entities, but this is far from the reality of cerebral processing.
Cognitive neuroscience follows another approach by trying to identify the biological basis of psychological processes. Similar to cognitive psychology, in the beginning cognitive neuroscience focused mainly on the examination of cognitive functions. While electrophysiological research gives insight in the temporal dynamics of biological processes, functional imaging gives more insight in the spatial distribution of brain regions involved in cognitive processes. However, both methods face the methodological problem that in the end they follow a correlational approach, arguing that cognitive processes and behaviour have a temporal correlation with the observed biological signal.
However, regarding the definition of emotion things seem not to be so clear-cut. Emotions differ from 'cold' cognition by not only having a psychic facet but often also a somatic facet, for example changes in heart rate, blood pressure etc. As Ortony et al. [6] write, "The visceral sensations accompanying emotions

dieser Zustände selbst, aus dem erst unsere abstrahirende Analyse die einzelnen aussondert."

and the expressive manifestations of emotions are perhaps the two characteristics that must set emotions apart from other psychological states and events". It is one of the on-going discussions, whether emotions are primarily defined by the somatic or the psychic phenomena. The most famous hypothesis, suggesting that somatic changes cause emotions comes from James [7], who states, "that the bodily changes follow directly the PERCEPTION of the exciting fact, and that our feeling of the same changes as they occur IS the emotion". In contrast, cognitive psychology suggests that especially psychological processes are responsible for the emergence of emotions, mainly the process of appraisal. In some models appraisal is seen as a functionally essential part of cognition, and can be successfully integrated in existing computational models of cognition creating a unified model of cognition and emotion. [8]

Another obstacle when examining emotion is the introspective aspect, often referred to as "feeling". 'Feeling' has some overlap with the Qualia-problem in the debate of consciousness. "There is yet to know no known objective measure that can conclusively establish that a person is experiencing some particular emotion, just as there is no known way of establishing that a person is experiencing some particular colour." [6] The incongruent use of the terms 'emotion' and 'feeling' causes a lot of confusion. In the earlier quotation from James, feeling could also be translated as a perception of changes in the inner state of the body. 'Emotion' is also used to describe, both the psychic (introspective) and somatic (bodily) aspect.

Another on-going debate is whether all emotions are equal or if there are basic and higher emotions. The idea of the existence of basic emotions is partially based on the work of Ekman [9], who extensively examined emotional expression in human faces, but goes back to Darwin's research on emotion [10]. The described emotions, anger; anxiety; disgust; fear; happiness; sadness and surprise do not cover the richness of human emotions such as love, grief, envy etc. While some cognitive psychologists support the concept of basic emotions [2] others argue that this distinction is based on false analogies [6] or that there is no consistent and specific somatic signature, including facial expression or cardiovascular, hormonal or other physiological change, which would allow us to separate basic from other emotions [11].

Affective neuroscience

Using the same technics as cognitive neuroscience, affective neuroscience emerged. Here the problem of temporal correlation between psychological processes and physiological processes becomes even more puzzling. This is mostly because of the introspective aspect of emotions, which in the end cannot be controlled during an experiment, but depends crucially on the ability of the examined subject to report his feelings. Thus, the repeated finding that the amygdala is involved in the processing of faces with mainly negative emotional expressions as anger, fear and sadness [12], gives no clue to the emotional experience partic-

ipants have at that moment.

Most people would state, in accordance with several researchers that animals are creatures with much less cognitive capabilities than humans, but that animals differ not so much from humans with regard to emotions. For example, Panksepp [13] states in his argumentation for the role of affect in neuroscience, "that emotional processes, including subjectively experienced feelings do, in fact, play a key roles in the causal chain of events that control the action of both humans and animals". Thus, animal research could give insight in underlying biological processes associated with behaviour similar to that observed in humans experiencing emotions/feelings. Not everybody has supported this view. The authors [11, 14] of two recent articles, targeting the theory of emotion from completely different perspectives, both more or less reject the transfer from animal to human emotions. Barrett [11] focussing on human emotions argues that emotions are not solely explainable by the bodily changes and possibly subjective states, but can be only manifest in social relationships, which constitute a framework in which the observable changes become meaningful to the observer. In contrast, LeDoux [14] argues that the term emotion should be avoided in animal research, because this term implies that the subjective part of human emotions is analogously present in animals. He instead proposes to look for behaviour related to survival in specific situations or behaviour to hold homeostasis and the underlying brain circuits. From these analogues to human behaviour could be drawn.

Keeping these problems in mind it becomes even more puzzling to examine disturbed or impaired cognitive and emotional functions, which are present in psychiatric disorders. Thus, in first place, it seems more likely to investigate healthy controls, with respect to the relationship between cognition and emotion, and the underlying biological processes.

Interaction of cognition and emotion in healthy subjects

Not surprisingly in the line of the findings described above, in the last years possible interactions between cognitive functions and emotion have been examined. There are two basic approaches, one is the induction of mood before or during the experiment, for example by presenting emotional pictures [15, 16], film clips [17] or music [18]. The other is that stimuli, for example words [19, 20] or pictures [21], which have to be memorized or are used in an emotional Stroop task, vary with respect to their emotional impact.

A recent review [22] has shown that performance in cognitive tasks was modulated by moods induced 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 size was small especially compared to the high effect size for self-experienced emotion. This finding may be explained by varying effects of different emotions, but also by varying effects of mood induction on different cognitive functions. Induction of positive mood before recall of a list of words presented prior to the mood induc-

tion increases recall [23]. In addition, positive mood has a facilitating influence on verbal working memory but a negative influence on spatial working memory. For negative mood, the influence on verbal and spatial working memory was vice versa [24]. Mood induction affects reaction time and error rates differently in an AX continuous performance task that examines sustained attention [25]. In an elegant study performed by Martin and Kearns [26], effects of positive mood induction on working memory capacity and selective attention are examined in the same group. While positive mood induction reduced working memory capacity, selective attention was not affected, neither in a Stroop nor in an Erikson Flanker task.

Many studies have been performed to examine the effect of emotional stimuli on cognitive functions such as memory [27-29], working memory [30-32] and attention [33-35]. The basic difference to the previous approach of inducing mood is that the stimuli self are supposed to elicit an emotion, which should not last to long, to guarantee that the consecutive presented stimulus can cause its own effects. From the results of the manifold of studies it seems clear that there is an effect of emotional stimuli on memory and attention. The effects on working memory are less clearly demonstrated. Several studies have shown that long term memory for emotional pictures (mostly from the International Affective Picture System [36]) and faces with emotional expressions is better than for neutral pictures [21, 28, 29, 37, 38] or faces with a neutral expression [39, 40]. Similar effects have also been found for verbal emotional stimuli, which were found to be better remembered in several studies [41, 42]. However, one of the unresolved questions is which specific properties of emotional stimuli are responsible for the emotional memory enhancement [43]. Schmidt et al. [32] reported that item recognition is highest for highly arousing positive items and lowest for low arousing positive stimuli, with negative stimuli in between, suggesting an interaction between arousal and valence. In contrast, contextual information is only influenced by arousal, the more the better, and valence has no influence. In addition, the design of studies (free recall vs. recognition, implicit or explicit memory) seems to influence the observed effect [44]. Thus, it is still debatable which properties of emotional stimuli cause the better memory performance for these stimuli, and for this reason the concept of emotion memory enhancement may be to broad.

Similarly, the question to what extent emotional stimuli influence attention raises contradictory results. There are different experimental designs to explore the effects of emotion on attention. Attentional blink describes the phenomenon that when two stimuli, which have to be attended, are presented with a short (smaller than 500 ms) stimulus onset asynchrony (SOA) the second stimuli is more difficult to attend. This effect is enhanced when the first stimulus is a taboo word [45] and decreased when the second stimulus is a negative word with high arousal level [46]. Pictures from the IAPS system compete with the attentional resources necessary for the solving of a mathematical problem or the detection of a line above or below the presented picture [47]. For certain classes of stimuli, such as

faces and pictures, it seems that they are evaluated for their emotional meaning [48] very early and therefor have the ability to grasp attentional resources very early. More abstract stimuli such as emotional words seem to attract more attention only when lexico-semantically processed [49], associated with differences in late positive components of event-related potentials (ERP). In this study, this is true for positive compared to negative and neutral nouns. In a visual search task with schematic faces, threatening faces were detected faster than faces with neutral, happy or other emotional expression [50]. However, when photographs of human faces with emotional expressions were used as stimuli the opposite effect was found, happy faces were detected faster and with higher accuracy [51]. The contradictory results from these studies raise a very important and often underestimated concern, namely that the differences in behaviour are not based on the emotional differences between the stimuli, but on differences in other stimulus properties, in that case schematic versus real faces.
Another way to examine the influence of emotion on attention is the emotional Stroop task. Again, contradictory results are reported in healthy subjects. While in some studies [52] no effects of emotional words could be detected, others reported increased reaction times of negative [53] or taboo words [54]. However, study design, especially mixed versus blocked presentation of word categories, seems to be of major relevance [55, 56], with stronger effects in the blocked presentation version.

Schizophrenia

It was at the same time that Wundt formulated his ideas about physiological psychology that schizophrenia emerged as a new psychiatric entity. The two major concepts were developed by Kraepelin [57] and Bleuler [58]. Kraepelin focused on the cognitive disturbances in schizophrenia, brought him to introduce the disorder as ‘dementia praecox’. Bleuler, who introduced the term ‘schizophrenia’, considered disturbances in emotional processing (namely ambivalence, autism and disturbances of affect) as part of the basic features of schizophrenia.
The start of schizophrenia at an early age makes schizophrenia the most devastating psychiatric disorder, often leading to reduced occupational and social functioning as expressed in a high rate of patients living without partnership, frequent unemployment or working below educational level [59] and finally a seriously reduced life expectancy [60].
Not only schizophrenia, but all psychiatric disorders are characterized by disturbances in cognitive functions, emotions and behaviour, with different emphasis on one of the three domains. But while several psychiatric disorders show disturbances only during the acute phase of the disorder, for example during a depressive episode or a panic attack, in schizophrenia [61, 62] or bipolar disorder [63] disturbances in cognitive functions are permanent. With respect to emotion processing there is less evidence for lasting disturbances in both schizophrenia [64, 65] and bipolar disorder [66].

This thesis

This thesis approaches the relation between emotion and cognition from different perspectives. The first part focuses on the neurobiological aspects in healthy individuals. By using functional magnetic resonance imaging different aspects were examined with the focus on identifying neurophysiological processes underlying the psychological phenomena.

As both cognitive and emotional disturbances are present in patients with schizophrenia the second part of the thesis addresses the question whether patients with schizophrenia perform differently on tasks examining the effects of emotion on cognitive functions than healthy controls. In addition, we addressed the, whether observable impairments were independently found in both areas (cognition, emotion) or whether there were effects over and above the individual deficits, suggesting an additional deficit, which only comes apparent when cognitive and emotional performance is examined in conjunction. To allow a more general view to this question, different domains were examined: working memory; attention and social cognition

Neuroimaging studies

Pain and emotion

In the second chapter the influence of depersonalisation on the processing of pain is examined.

The experience of pain comprises not only perceptual properties about intensity, localisation and temporal sequence, but also an affective property. It has been shown by neuroimaging studies that experimentally induced pain activates a pattern of brain regions including the somatosensory cortex, the secondary somatosensory cortex, the insula, the anterior and posterior cingulate cortex and the parietal cortex [67-73], described as the 'pain matrix' [74]. In addition, some studies found increased BOLD signal to painful stimulation in the amygdala and/or the orbitofrontal cortex [67, 75-79] demonstrating the involvement of limbic structures next to the ACC in the processing of painful stimuli. A recent meta-analysis [80] confirmed the role of the amygdala in experimental as well as clinical pain studies: in most of the studies increase in BOLD-signal to painful stimulation, but in several studies decrease in BOLD-signal. Additionally, the authors [80] conclude from their analysis that different sub-regions of the amygdala are involved during experimental induction of pain in healthy subjects and in patients suffering from pain caused by osteoarthritis, neuralgia or irritable bowel syndrome. It has been proposed earlier that the perceptual and the affective dimension of pain are represented in different brain regions [79, 81, 82]. This hypothesis has been further tested by several investigators with Positron-Emission-Tomography (PET) [83-85] using hypnotically induced changes in the perception of pain intensity and pain (un)pleasantness. Indeed the results of these studies suggest that partly independent systems process the sensory dimension and affective dimensions of

pain. For the sensory dimension these would comprise somatosensory regions [83] and for the affective dimension of pain comprising the ACC [84].
When there is a specific system for the affective dimension of pain, two questions arise. Can mood induction influence the experience of acute or chronic pain, and how could this mood induction been accomplished. Indeed, in several studies the direct influence of emotion on pain experience has been reported. Pictures that evoke fear and disgust decreased pain tolerance and increased experienced pain intensity and unpleasantness [86]. In another study [87] using pictures from the IAPS [36] differential effects of positive, neutral and negative pictures were found. Highest pain tolerance was present when positive pictures were presented. Compared to neutral pictures, the effect of positive pictures on pain tolerance (increase) was higher than that of negative pictures (decrease). Similar results were obtained by Godinho et al. [88] demonstrating that pictures with negative content increased the subjective unpleasantness of painful stimuli in participants, especially when negative pictures displayed body related content, such as wounds etc. were presented. In addition, the increase in subjective unpleasantness was associated with an increase of the amplitude of the somatosensory evoked potential.
FMRI studies call the hypothesis that there are two different systems, representing the affective and sensory dimension of pain, into question. When attention to pain is modulated by an adapted counting Stroop task during painful stimulation [89], a reduced BOLD-signal is found in areas associated with the sensory (thalamus, cerebellum, premotor cortex) and affective dimension (anterior and posterior cingulate gyrus, insular cortex) of pain. At the same time parts of the orbitofrontal cortex and perigenual cingulate cortex showed higher BOLD-signal changes, which are suggested to reduce subjective pain experience, which corresponds to the subjective reduction of pain during attentional distraction in the interference condition of the Stroop task. The same increase in BOLD-signal in the orbitofrontal and cingulate gyrus has been found when applying a colour-word Stroop task during painful stimulation [90], but different effects were seen with respect to the pain matrix. The primary sensory cortex and the posterior insular cortex still showed increased BOLD-signal during painful stimulation and simultaneous execution of the Stroop task, demonstrating a modulation of the affective dimension of pain by distraction of attention. Other studies demonstrated effects of emotion modulation either by odours [91] or the presentation of IAPS stimuli [92] during painful stimulation. Bad odour, as negative emotion inductor, increased BOLD-signal changes in response to painful stimuli compared to good odour as positive emotion inductor, in regions associated with both the affective (anterior cingulate gyrus) and the sensory (somatosensory cortex and thalamus) dimension of pain. However, on subjective level only pain unpleasantness but not intensity was increased when bad odour was delivered during painful stimulation. Furthermore, paying attention to the painful stimulus in the absence of odour changed BOLD-signal only in the anterior insular cortex accompanied by increased pain intensity and unchanged pleasantness. The presentation of neg-

ative IAPS stimuli [92] during painful stimulation at first glance also increases BOLD-signal also in regions primarily associated with the sensory dimension of pain (paracentral lobules and insular cortex), suggesting that primary sensory regions (paracentral lobules) are influenced by emotional modulation (higher BOLD-signal in negative condition). IAPS stimuli had also a differential influence on the R III reflex, an electrophysiological measure and an indicator for spinal nociception. Unpleasant stimuli increased the amplitude of the R III reflex significantly compared to neutral and pleasant stimuli. When the differences in pain ratings (significantly higher during presentation of unpleasant compared to neutral and pleasant stimuli) were correlated with BOLD-signal changes, however, only the insular cortex showed significant results. Much stronger correlations were found for the differences of the R III reflex between the unpleasant and the other stimuli in the bilateral amygdala, ventromedial and medial prefrontal regions and the subgenual anterior cingulate gyrus. The authors [92] suggest that these regions – influenced by the emotion evoked by the unpleasant stimuli, are involved in the top-down modulation of spinal projections to the cerebrum, resulting in a different experience op the painful stimuli. No differences were made in ratings between pain intensity and unpleasantness, thus conclusion about a different modulation of the two suggested systems cannot be drawn.

In contrast to the studies of Rainville and Hofbauer [83, 84] that targeted the two dimension of pain directly via different suggestion, the studies referred to in the previous paragraph used a broader approach: attentional distraction [89] or emotion induction [91, 92]. Although the results from the latter studies do not contradict the two pathways model in a strict sense, they suggest that the two pathways are less independent as originally was suggested. Thus it seems that both cognitive and interventions with emotional stimuli may change both, the affective and sensory experience of pain.

The interpretation of results from studies intended to modulate pain experience either by distracting attention or changing the emotional context, in which painful stimuli are delivered, is complicated by the fact that emotion and attention are thought to involve different brain regions, which are of course in a different way anatomically connected with the brain regions of the pain matrix. Furthermore, parts of the pain matrix are also parts of the attentional brain network or have overlap with brain regions involved in the processing of emotion.

A recently published review summarizes that there are substantial commonalities between hypnosis and states of dissociation, including conversion system as sensory and motor impairments [93]. Patients with dissociation or traumatic experiences [94] report reduced pain experience, but this has been reported also in other patient groups [95]. Depersonalisation as a form of dissociation is characterized by changes of the experience of oneself or the environment and often with a loss of feelings of the own body and a profound inability to experience emotions [96]. It has been suggested by Sierra [97] that in patients with depersonalisation disorder the influence of the frontal cortex causes an inhibition of the limbic system.

A similar mechanism has been proposed by Mayberg et al. [98] for the aetiology of symptoms in depression. Patients with dissociative disorder rated IAPS stimuli with negative content as less arousing, associated with diminished skin conductance responses, a psychophysiological measures for arousal [99]. A FMRI study in patients with depersonalisation found a reduction of BOLD-signal increase compared to healthy controls when viewing IAPS stimuli with aversive content predominantly in the left hemisphere, including the insula, parietal and temporal cortex, the anterior and posterior cingulate gyrus and occipital cortex [100]. However, a PET study [101] found higher metabolism in the left parietal lobe (somatosensory and multisensory association areas) and the left occipital cortex (visual association cortex). Thus the underlying neurobiology of depersonalisation remains unresolved. However, processing of emotional stimuli affects areas, which overlaps with brain regions of the pain matrix, which are also influenced by the presentation of emotional stimuli and display changes in BOLD-signal when hypnosis is applied.
Patients with personality disorders, who inflict self-injury, frequently report that they don't feel pain while inflicting self-injury. As a model for this phenomenon, healthy participants highly susceptible to hypnotic suggestion were examined with FMRI. During three separate FMRI sessions pain stimuli were delivered in three different states of consciousness: 1. awake, 2. in hypnotic induced relaxation and 3. in hypnotic induced depersonalisation. Differences in BOLD signal between these states were evaluated to examine which brain areas responded differentially to the same pain stimulus during the three different states of consciousness. We focused on brain regions associated with perception, the cognitive aspect of pain, and those associated with emotion during the different states of consciousness.

Emotional Working Memory
In the third chapter differences in brain processing between identity and facial expression in a working memory paradigm were examined.
In animal research, the lateral prefrontal cortex [102] and the parietal cortex [103] have an important function in working memory (WM). Working memory is a widely examined neuropsychological function examined with FMRI. Indeed the above-mentioned regions show increased BOLD-signal during working memory performance using delayed match to sample paradigms [104, 105] or N-back paradigms [106, 107]. A meta-analysis of neuroimaging studies of working memory published several years ago [108] found that besides these two brain regions several other regions in the occipital and temporal lobe are associated with the successful performance of working memory tasks. According to Wager et al. [108], the increase in BOLD signal in certain brain regions depends on material of the task (spatial, object, verbal) or differences in task demand (pure storage vs. manipulation during delay). Most, but not all regions, have higher BOLD signal increases during paradigms that put demands on executive functions.

Working memory for faces forms a subcategory of object working memory. We examined facial working memory once in healthy volunteers only with FMRI (chapter 3) and in a behavioural task in patients with schizophrenia and healthy volunteers (chapter 6). After some early papers [109, 110] examining working memory for faces, renewed interest in this research questions arose with upcoming neuroimaging [111-116]. These studies mainly focused on the question whether specific regions could be detected for facial working memory. Haxby et al. [113] found that during maintenance of facial information changes in BOLD-signal were observed in the inferior and midfrontal gyrus, while during maintenance of spatial information mainly changes in the superior frontal gyrus were observed. In contrast, Rama et al. [117] found increase of BOLD-signal in the superior frontal gyrus and the intraparietal sulcus during maintenance of faces compared to voices. None of these studies focused on differences between neutral and emotional expressions or differences between identity and emotional expression and identity. Apart from our study presented in chapter 3 only two other studies examined facial working memory for identity versus emotional expression [118, 119]. Both studies found differences in BOLD-signal when the two conditions (identity vs. emotion) were compared. LoPresti et al. [118] found a higher change of BOLD-signal in the orbitofrontal cortex, firstly for the encoding for emotional faces and secondly for negative faces during retrieval, but these results are based on a region of interest analysis derived from a comparison between facial versus a neutral control condition with grey shades. The amygdala, another predefined region of interest, did not show differences in BOLD-signal change between the two conditions. Neta and Whalen [119] found differences between the two conditions with higher BOLD-signal changes in the frontal lobe and the superior temporal gyrus for emotional expression and in the precuneus and the anterior cingulate gyrus (ACC) for identity. Again, the amygdala showed no differences and additionally, in the frontal lobe and the ACC the parameter estimates had negative values. Thus the difference in these regions are based on a smaller decrease in BOLD-signal in the particular condition.

In addition, there are several studies which examined short term memory for faces with implicit modulation of emotion [114, 120, 121]. These did not investigate the contrast mentioned above but differences in BOLD-signal change with respect to different emotions. On the behavioural level, in all studies an advantage for faces with angry expression [114, 121] or emotional faces compared to neutral faces [120] was present. In all three studies a different number of brain regions showed increased BOLD-signal for the contrast of emotional compared to neutral faces. Overlapping brain regions between studies were the right superior temporal sulcus in two studies [114, 121], the right inferior frontal lobe [114, 121] and the right globus pallidus [114, 121]. Only Wolf et al. [121] found significant BOLD-signal increase for angry compared to neutral faces in the right extended amygdala. However the design of the three studies does not allow disentangling the stages of encoding, delay and retrieval, and thus it is not possible

to determine exactly the role of each of the detected brain regions.
In summary, it seems that the perception of emotional faces is partially based on the structures of the superior temporal lobe, besides the fusiform gyrus, which seems more responsible for the processing of faces irrespective of their emotional expression. An extensive review [122] confirms these results. Furthermore, from all studies it is clear that regions as the lateral prefrontal cortex and the parietal cortex are involved in facial working memory, but it remains unclear to what extent limbic structures as the amygdala are involved in the maintenance of faces with emotional expressions.
We examined working memory for emotional faces. For that reason a working memory task was designed with parametric load variation and two conditions, identity and emotion. During FMRI a group of healthy participants performed a forced-choice Sternberg-paradigm. Participants were asked to memorize either the identity or the emotional expression of 1, 2 or 3 faces presented in a sequence. We aimed to examine to what extent brain regions associated with cognitive processes and brain regions associated with emotional processes were involved differently in the identity or emotional expression task.

Performance monitoring
The fourth chapter describes the influence of verbal versus facial feedback in a time estimation task.
Essential to all living creatures is that changes in the internal and external environment make it necessary to adapt behaviour. Thus a plant growing towards the sun or a protozoan moving away from a threatening environment already show adaptive behaviour. However, adaptive behaviour has to be monitored with respect to the effects the adaptive behaviour achieves. Especially negative feedback is important, because it signals that recent behaviour was inappropriate to reach a certain goal. In humans, examination with electroencephalography has detected a characteristic signal for the processing of feedback, the feedback (FRN) – or error related negativity (ERN) [123]. The FRN represents the evaluation of the feedback with respect to its valence or motivational significance. Source localization studies suggested that the anterior cingulate cortex (ACC) is involved in the generation of the ERN [124]. Studies with fMRI confirmed that the ACC or the rostral cingulate zone (RCZ) [125], show increased BOLD-signal for errors compared to correct responses [126-128]. Furthermore, it has been shown that the magnitude of brain responses as measured by event-related potentials or changes in BOLD-signals is influenced by several factors: task instructions (when accuracy is emphasised over speed) [128], task difficulty (easy vs. difficult detection of errors) [129, 130] or the magnitude of prediction error [131]. However, results are not unequivocal, for example Falkenstein et al. [129] described an increase for the ERN the easier the error can be detected, while Maier et al. [130] described an opposite effect, an increased ERN for errors which are more difficult to detect. Regarding the focus of this thesis I will discuss mainly studies that examined the

influence of emotion on performance monitoring. Only a small number of studies addressed this question using FMRI [132-136] with heterogeneous paradigms and results. Many more studies addressed this question with electrophysiological methods, focusing on the ERN and the FRN. In an adapted Simon task with emotional faces as stimuli, internal error detection was associated with a higher ERN when happy faces were displayed compared to angry or neutral faces [137], and in addition a similar deflection of the EEG as the ERN was observed for correct trials. In contrast, Boksem et al. [138] observed a higher ERN for trials displaying disgusted faces compared to happy and sad faces, and the FRN for correct trials had lower amplitude than for erroneous trials. Again, in an emotionally modulated numeric Stroop task [139] correct responses were associated with a brain potential similar to the ERN, called conflict-related negativity (CRN). The highest amplitude of the CRN in this study was observed, when an aversive picture preceded an incongruent trial. The authors suggest that the emotional processing of the aversive stimulus competes with the cognitive processing of the incongruent stimulus. Other studies combined the presentation of a flanker task with the presentation of IAPS stimuli [140, 141]. Larson et al. [140] presented IAPS stimuli as background during a flanker task with letters. Arousing stimuli increased reaction times compared to neutral stimuli, but more important, the ERN amplitude was increased for errors in trials with a positive picture, compared to neutral and negative trials. In contrast, Wiswede et al [141] found an increase of the amplitude of the ERN for errors preceded by unpleasant IAPS stimuli. However, this effect was only present in the first half of the experiment; in the second half, the effect of stimulus valence was not present anymore. In addition, both studies presented the IAPS stimuli at different time points during trials, either preceding the flanker task [141] or using the IAPS stimulus as background of the flanker task [140]. This difference may have caused differential processing of the emotional stimulus, resulting in the contradictory effects on the ERN. Again, contradictory results were found in studies using the identical paradigm by inducing a negative affective state with derogatory feedback [142, 143]. Wiswede et al. [143] described that derogatory feedback delivered after thirty trials increased the amplitude of the ERN after trials with an incorrect answer, while encouraging feedback did not affect the amplitude of the ERN. Derogatory feedback was further associated with an increase in negative and a decrease in positive affect. In contrast, Clayson et al. [142] observed an increase in negative affect in both groups, whether they received encouraging of derogatory feedback. The latter study [142] could not replicate the finding of an increase in amplitude of the ERN after derogatory feedback [143] in a much bigger sample. Similarly, Ogawa et al. [144] reported a decrease of the amplitude of the ERN as a consequence of negative verbal feedback while participants performed a spatial Stroop task. Also positive feedback reduced the ERN compared to no feedback, but to a lesser extent than the negative feedback.

Healthy controls either characterized as helpless or not helpless, based on the

results of a specific questionnaire, differed significantly in the ERN amplitude, evoked by a flanker task. Differences between the ERN amplitude to erroneous and correct responses was bigger in the helpless group than non-helpless group [145]. In participants labelled as high and low anxious a different effect was observed [146]. Here faces with emotional expressions were used as feedback stimuli. In one condition (positive context) happy faces represented positive feedback and neutral faces negative feedback, in the other condition (negative context) neutral faces represented positive and angry faces the negative feedback. Neutral faces elicited enlarged amplitude of the early component of the FRN when they represented negative feedback as compared to the case in which neutral faces represented a positive feedback. In addition, positive context caused bigger differences in the early component of the FRN between positive compared to negative feedback than it was present in the negative context. Importantly, no differences between the two groups were observed. In contrast, differences between groups were found in the fronto-central generated late component of the FRN. In the low anxious group neutral faces elicited much bigger amplitude in the positive compared to the negative context condition, but this effect was not found in high anxious participants. Both groups had no differences in amplitude between positive and negative feedback in the negative context condition. Recently, Schulreich et al [147] used the same paradigm as in the study presented in chapter 4 [136] in an electrophysiological study. However, abstract (X,O) symbols were compared to faces as feedback. The FRN amplitude was significantly higher for negative and for facial feedback, but there was no interaction between these main effects.
In conclusion, from the here presented studies the effect of emotion on the amplitude of the ERN and FRN remains unresolved. Importantly, increases in the amplitude of the ERN and the FRN are not only the result of error processing, but are also observed as a consequence of positive feedback. To what extent an increase or decrease of the amplitude of these potentials is caused by an additional use of neuronal resources or a competition between emotional and cognitive processes cannot be answered on the basis of these results.
While studies using electrophysiology profit from the high temporal resolution, the advantage of FMRI is to detect the brain regions involved in performance monitoring. As already mentioned above, the rostral cingulate zone is a region involved in performance monitoring, together with the medial prefrontal cortex, the insula region and other regions of the anterior cingulate gyrus. Some of these regions have also been found to be involved in processing of emotional stimuli [148, 149]. Jimura et al. [150] examined the effect of different feedback types after the switch of the relevant dimension during a Wisconsin Card Sorting Task. The authors suggested that negative feedback given after the instruction to switch to a new stimulus dimension would induce a negative emotion compared to a neutral feedback given under the same circumstances. Indeed, negative feedback caused increase of BOLD-signal in the medial PFC compared to the neutral stimulus. Verbal feedback, together with the delivery of either sweet juice or a bitter

solution, was provided during a time estimation task for periods between 6.5 and 13 seconds [151]. Participants were told that the feedback either was given by a computer or by person, and that the best team (participant and feedback provider) would receive a financial award. The latter condition was meant to implement a social component. In fact, a computer always produced feedback. Comparison between negative and positive feedback revealed higher BOLD-signal in the basal ganglia for positive feedback and higher BOLD-signal in the RCZ and the subgenual cingulate for negative feedback. More important the interaction between feedback and the computer vs. social condition revealed two regions, the anterior ventromedial PFC with a higher BOLD signal for positive feedback in the social condition and the subgenual cingulate with higher change in BOLD signal for negative feedback in the social condition. In two groups, defined as high or low depressed, feedback related brain activity during a motion prediction task was examined [133]. Negative feedback increased BOLD-signal compared to positive feedback in the posterior medial prefrontal cortex, partially overlapping with the RCZ. A consecutive region of interest analysis of this signal increase showed that the highly depressed group had a higher signal increase than the low depressed group. The authors suggested that the posterior medial PFC is not only involved in error processing but also in the processing of emotional aspects of feedback. Conscious affect regulation was used to examine the influence of emotion on feedback related brain activity [132] Participants were instructed to react either: normally; becoming angry or to stay calm to an error made during a continuous performance task. With a conjunction analysis, the authors found that the BOLD signal, increased by errors, was modulated by the emotion induction in the dorsal ACC, with the highest BOLD-signal change in the anger condition and the lowest in the calm condition. In contrast, errors decreased BOLD-signal in the rostral ACC, but again the anger condition had the strongest influence on the BOLD-signal.

In conclusion, studies using FMRI supports the findings from electrophysiological studies that the rostral cingulate zone has an important role in feedback processing. In addition, these regions seem to be mainly involved in the processing of negative feedback. However, other regions show increases of BOLD signal to feedback processing, such as the basal ganglia to positive feedback. Emotional modulation of feedback influenced BOLD signal changes in the medial prefrontal cortex. Feedback related increase of BOLD signal in the RCZ is modulated by levels of depressed mood and during evoked changes of affect. The interpretation of these results is complicated by the fact that the regions involved in feedback processing are also involved in the processing of emotions.

To further evaluate the influence of emotional feedback, we examined the effects of verbal compared to facial feedback in a time estimation task.

A group of healthy participants were asked to estimate the duration of one second during FMRI measurement. They received feedback on their estimation by either verbal feedback or by the presentation of emotional faces. Happy faces indicated

a correct estimation and anxious faces indicated an incorrect estimation. By using faces, ecological more valid stimuli were used than with verbal stimuli, which may be processed in a more cognitive manner. Again, we focused on the question to what extent brain areas associated with the processing of emotional faces would be involved during the completion of this task.

Attention and emotion

In the fifth chapter the influence of romantic love on attention and associated brain activation was examined in visual oddball-paradigm.

Attention can be examined in many different ways. One of the frequently used paradigms is the oddball paradigm [152], especially in conjunction with electrophysiological methods. The standard oddball task (visual or acoustically) comprises infrequent stimuli (target) embedded in a train of frequently presented stimuli (standard). An extended version comprises additional infrequent novel/distractor stimuli. Typically, participants are asked to silently count or react with a button press to the target stimuli. Many studies have shown that target or novel stimuli in the oddball paradigm elicit a positive deflection of the EEG called "P300" [153]. In contrast to potentials preceding the P300, suggested to represent perceptual processing of stimuli, the P300 is suggested to represent higher cognitive processes. It has been shown that the P300 can be subdivided in an early P3a and a somewhat later appearing P3b, which show a differential spatial distribution over the skull. The P3a has its maximum amplitude over frontal regions, while the P3b shows its maximum amplitude over centro-parietal regions. Furthermore, the P3a is related to the processing of novel/distractor stimuli, while the P3b is related to the processing of target stimuli [153]. Taking all these different findings into account together with findings from lesion studies and other neuropsychological domains it has been suggested that the P3a represent primarily attentional processes ("orienting") while the P3b represents context-updating operations and memory related processes [153].

While originally oddball paradigms were used in electrophysiological studies, upcoming techniques as MEG and fMRI used oddball paradigms, especially focusing on the brain regions, which could be seen as the possible generators of the P300. Several studies have been done to identify brain regions with increased BOLD-signal to target stimuli compared to standard stimuli [154-156]. All of them found the temporoparietal junction, the insular cortex, and the medial prefrontal cortex, including the ACC involved in the processing of target stimuli. Brazdil et al. [154] and Gur et al. [155] found that also subcortical regions as the thalamus and the caudate nucleus were involved in the processing of target stimuli. Studies including novel or distractor stimuli [155, 157] found that frontal lobe regions are mainly involved in the generation of the P3a, though also the supramarginal gyrus and the inferior parietal lobe show increased BOLD-signal to novel/distractor stimuli [158].

In the last decade the influence of emotion on attention has been examined using

oddball paradigms with both electrophysiology [159-162] and FMRI [160, 163-166]. Most studies used stimuli of the IAPS [36], which were sometimes presented as targets [159, 162, 163] but mainly as novel or distractor stimuli [161, 163-166]. All electrophysiological studies using emotional stimuli as targets found an increase of amplitude of the P3b to emotional stimuli, but this seems to be mainly caused by the arousal these stimuli evoke, while no specific valence effects were found. This finding was especially intriguing for sexual arousing stimuli, which caused a significant increase of the P3b compared to all other stimulus categories [159]. However, when IAPS were used as novel stimuli, emotion did not affect the P3a, while the P3b again showed higher amplitudes for emotional stimuli (independent from valence) compared to neutral stimuli [161]. Campanella et al. [160] used faces as targets, which either differed in identity or emotional expression from the standard stimulus (neutral face). Amplitude of the P300 did not differ between the different targets (neutral, fearful or different identity), but latency of P300 was significantly longer, just as reaction time to faces with different identity. The lack of effect of emotional expression on P300 amplitude may be a consequence of small differences of arousal between the different stimulus types. In a series of studies, Yamasaki et al. [166] and Wang et al. [164, 165, 167] used IAPS stimuli as novel/distractor stimuli in a standard visual oddball task. Sad or unpleasant stimuli caused compared to targets and neutral stimuli increase of BOLD-signal in the amygdala [164-167], ACC [166, 167], ventromedial PFC [164, 165], the IFG [166, 167] and extrastriate visual regions [164-167]. The latter probably due to the enhanced visual complexity of IAPS compared to the oddball stimuli. Target stimuli caused increased BOLD-signal in fronto-parietal regions as the MFG, ACC and supramarginal gyrus described earlier [158]. Fichtenholz et al. [163] used IAPS stimuli as novel/distractors but also as targets in a visual oddball paradigm. Aversive stimuli increased BOLD-signal in the amygdala, IFG and extrastriate visual areas, irrespective of whether they were targets or distractors. As expected, aversive IAPS stimuli caused higher BOLD signal in the target relevant brain regions (IPS, SMG, MFG) when they were targets, but BOLD-signal also increased for neutral IAPS-stimuli compared to distractor stimuli in these regions, when aversive IAPS-stimuli were targets. The most relevant modulation of BOLD-signal was found in the cingulate gyrus. Separated in an anterior and posterior part, aversive stimuli increased BOLD-signal as targets and distractor in the anterior part of the cingulate gyrus, but significantly more pronounced in the target condition. Both, the anterior and posterior part of the cingulate gyrus showed increased BOLD-signal preferentially to the target stimuli irrespective of its property. One study used faces as standard and target stimuli [160]. BOLD-signal associated with target detection was increased in the inferior parietal and the mid frontal brain, but similar to the ERP results were not modulated by the emotion or identity. Fearful faces increased BOLD-signal compared to the other targets in the left fusiform gyrus, when individual ERP amplitudes were used as additional regressor, and in the right fusiform gyrus and left supe-

rior orbitofrontal gyrus, when individual ERP latencies were used as additional regressor. Happy faces increased BOLD-signal compared to the other targets in the left posterior cingulate gyrus and right parahippocampal gyrus, when individual ERP amplitudes were used as additional regressor and in the right insula and left caudate nucleus, when individual ERP latencies were used as additional regressor. Target faces with different identity than the standard face showed the most distributed BOLD-signal changes in the frontal, temporal, parietal and the occipital lobe, and the insular and the cingulate gyrus, when individual ERP amplitudes were used as additional regressor. When individual ERP latencies were used as additional regressor, this comparison revealed higher BOLD-signal in the right hippocampus and parahippocampal gyrus.

Summarizing the results there is evidence that emotion-modulated attention is associated with changes in brain activation. Negative emotional stimuli used as novel/distractor stimuli increase BOLD signal in the medial prefrontal, temporal and occipital cortex [165, 166]. Sad stimuli used as novel/distractor stimuli increase BOLD signal in the medial prefrontal cortex and the amygdala [164, 167]. In contrast, target stimuli elicited another pattern of BOLD signal increase, comprising the cingulate, parietal and lateral prefrontal cortex, suggesting that different brain systems process the emotional aspect of stimuli and the attentional demand of the task. On behavioural level results are inhomogeneous. Participants reacted significantly slower to negative emotional novel/distractor stimuli [165, 166], suggesting that negative emotional content binds attentional resources. However, when negative emotional stimuli had to be attended explicitly, reaction time differences between negative and neutral emotional stimuli disappeared [163]. In addition, differences in BOLD-signal between negative and neutral stimuli were smaller in this condition, compared to a condition, in which a geometrical stimulus had to be attended. The results of Campanella et al. [160] point in the same direction. While differences in emotional expression of target faces had no effect on response latency, changing the identity of the face increased response latency significantly, associated with an increase of BOLD-signal in more distributed pattern. Differences in BOLD-signal changes between emotional conditions [160] were not detected in regions typically found in oddball studies, again suggesting that emotional properties and the attentional task demand are processed in different brain systems.

However there are some methodological considerations, which complicate the interpretation of the results. For instance the presentation time (1500ms) of IAPS stimuli in the studies of Wang et al. [164, 165, 167] is much longer than in a typically oddball task (for example Bledowski et al. [157] 75 ms, Campanella et al. [160] 500ms), which allow participants to engage in other than attentional processes. The effects of probability and similarity of stimuli has been received little attention in studies using FMRI, although is has been demonstrated that both aspects affects the amplitude of the P300 significantly. Thus, to what extent the above described FMRI studies correspond with the effects of emotion on the

P300 needs further examination. A previous study [168] has shown that the P300 is modulated differentially by emotion related and task related attention. The study presented in chapter 4 aimed to further elucidate the electrophysiological finding of Langeslag et al. [168] with FMRI.

As romantic love, a specific kind of emotion, and its influence on attention is the topic of chapter 5, a closer look at the literature concerning the neurobiology of romantic love is necessary. Love is one of the most intense emotional experiences one can have. Several studies have examined romantic love using FMRI [169-175], and two ERP studies [168, 176] have been performed. Although beyond the scope of this discussion, the neurobiology of other kinds of love, e.g. maternal love [177, 178] or unconditional love [179] have also been investigated. All studies used a broadly similar approach. Participants were asked to look at pictures of the beloved person and at control stimuli. BOLD-signal changes based on the contrast of the two conditions were detected in widely distributed brain areas. These included: parts of the medial and lateral frontal cortex [171, 173, 175], the cingulate gyrus [169-171, 173, 175], the insular region [169-171, 173, 175], the hippocampus and parahippocampal gyrus [169], the amygdala [169-171] and in subcortical areas associated with the processing of reward as the central tegmental area, the hypothalamus and the caudate nucleus [169-173, 175, 180]. When either the names of the beloved person or a friend were used as subliminal priming during a lexical decision task, many of the above mentioned regions showed increased BOLD-signal to trials preceded by the name of the beloved as compared to the friend's name [174]. In addition, in subjects unhappily in love [175] or recently rejected by their partners [173] similar patterns of regions with increased BOLD-signal were found when looking at pictures of the beloved person. Stoessel et al [175] even found that BOLD-signal increases stronger for erotic pictures than for pictures of the beloved person in participants happily in love and in the group of unhappily in love vice versa, which may be interpreted as a stronger feeling of being drawn to the beloved person in the unhappy group. The involvement of brain structures suggested to mediate reward has given reason to propose that romantic love is more than an emotional state but a motivational state [169, 170, 172, 173].

We used the same paradigm used in a previous study [168]. Pictures of the person with whom the examined subject had fallen in love recently and pictures of a good friend were used as target stimuli or to be ignored stimuli embedded in a stream of pictures of an unknown face. The study examines the modulation of attentional processes by the emotional stimuli, which have to be consciously attended, when the beloved one is the target, or unconsciously ignored, when the friend is the target stimulus. With this design the neurophysiological processes associated with the modulation of attention in comparison between two different states of affection could be analysed.

Studies in patients with schizophrenia

In general, patients with schizophrenia display deficits when tested on different domains of higher cognitive functions, such as sustained attention [181], executive function [182], working memory [183], language [184], explicit and implicit learning [185] and memory [186].

There is a long lasting discussion whether these deficits are restricted to certain domains as mentioned above or whether there is a general cognitive deficit [187] (see [187]) and there is much evidence that indeed all cognitive domains are impaired with moderate to strong effect sizes [188, 189]. However, there is a great variability in the number of domains impaired in patients, raising doubts with respect to a general deficit. Raffard et al [190] investigated different domains of executive function (inhibition, updating, set shifting, divided attention) in chronic SC and found that the patients as group demonstrated an overall deficit, but when results were further specified per individual, some were impaired in only one domain and others in all domains..

Next to cognitive impairments, disturbances in emotions are suggested to be a core symptom of schizophrenia, reaching back to the conceptualization of the "group of schizophrenias" by Bleuler [58]. Bleuler emphasized that due to the differences in appearance and course, schizophrenia should not be considered as a single disorder, but as a group of disorders. However, he defined several symtoms, which he suggested to be the core symptoms being present in all forms of schizophrenia, the loss of association, a loss of affective modulation , ambivalence and autism.

However, as pointed out by Kring and Caponigro [191], the term "emotion" is as broad as cognition and therefore comprises many different components: an intra-psychic experience (happiness, sorrow), appraisal (labelling the self-experience and its suggested cause) a bodily or facial expression (a smile, puckered brows), physiological changes (changes in heart rate and skin conductance), hormonal changes (increase in cortisol) and not to forget changes in the central and peripheral nervous system.

In all studies involving patients, only patients with recent-onset schizophrenia were included. Recent onset is defined as the first five years after the appearance of the first symptoms, which were in most cases prodromal symptoms as anhedonia, social withdrawal, lack of energy etc. The inclusion of this specific group is partially due to the fact that at the department of psychiatry at Erasmus MC an early psychosis unit is located. This situation provides the opportunity to investigate patients, who are medication-naïve, medication free, or have only little exposure to antipsychotics, which excludes chronic use of antipsychotics as serious confounders. In addition, effects of a long duration of schizophrenia itself with all the negative consequences on physical health and social and occupational aspects are not present in this population. However, the results of the studies can therefore not be generalised to patients with schizophrenia in general, although impairments in cognitive functions have been found to be stable over the time

course of the disorder.

Emotional working memory

In the sixth chapter differences on behavioural level in a facial working memory task between patients with schizophrenia and healthy controls were examined.

In patients with schizophrenia, a great amount of studies investigated the ability of patients to recognize emotion in human faces. Many studies have demonstrated that patients with schizophrenia have impairments in the recognition of emotions [192-196], but this seems predominantly true for negative emotional expressions, but not for positive emotional expressions [197, 198]. In a recent study [199] even no differences have been found for the recognition of emotion between patients with schizophrenia, but intensity of the displayed emotions was underestimated by patients compared to healthy controls, but did not differ for the six displayed emotions. In contrast, Yu et al. [200] report the opposite, significant impairments in the recognition of the majority of facial emotion, but no difference compared to healthy controls with respect to the intensity of the displayed emotions. A recent meta-analysis [201] concluded that deficits in emotion recognition in patients with schizophrenia are severe, but the authors also admit that the effect sizes of the included studies varied substantially, based on methodology and demographic characteristics. Furthermore, as mentioned by the authors, a general impairment in facial processing may underlie this finding, and thus not specific for emotional expressions.

However, the description of early visual impairments in patients with schizophrenia [202, 203] raised the questions about the effects of this impairment on emotion recognition. Indeed from behavioural as well as electrophysiological results comes evidence that early stage visual deficits may account for some of the observed emotion recognition deficits in patients with schizophrenia. Detection of contrast predicts the discrimination of fearful faces [204] and the N170, a electrophysiological correlate of the structural encoding differentiates patients with schizophrenia from healthy controls, but not the N250, a electrophysiological correlate of affect modulation [205]. In a recent study [197] evidence is found that the magnocellular pathway, one part of the visual system relevant for the spatial information of an object [206], is specifically impaired. In this study [197] it could be shown that contrast sensitivity for low spatial frequency, processed via the magnocellular pathway, is impaired in patients with schizophrenia, and that visual evoked potentials (VEP) sensitive for the magnocellular pathway reached a significantly lower signal-to-noise-ratio in patients compared to healthy controls. Individual values of VEP and contrast sensitivity for low spatial frequency were significant predictors for the emotion recognition. In a pure behavioural study [207] these findings are partly confirmed by demonstrating that for the recognition of individual emotions in human faces patients with schizophrenia rely on information derived from other spatial frequencies than healthy controls. In addition this information is drawn from different parts of the human face.

From studies examining visual scan paths during viewing emotional faces [208-210] there is additional evidence that patients with schizophrenia have impairment in the employment of a global viewing strategy, together with attentional impairments. These are suggested to be in part responsible for the impairments in emotion recognition, which may further be influenced by severity of symptoms [208], the depicted emotion [208, 210] or the context in which the face is depicted [209]. Thus even at the level of recognition of emotion there is strong evidence that cognitive aspects as perceptual impairments, attention and exploration strategies are involved.

Impairments in working memory function are a recurrently reported in patients [183] as well as impairments in the recognition of emotion in faces (see paragraph above). We described in chapter 6 of this thesis our results of a WM paradigm in which either the identity or the emotional expression had to be remembered over a short period of time. We aimed to investigate the influence of emotion on WM performance in patients with schizophrenia and healthy controls. There are several other studies, which focused on the interaction between emotion and working memory, using behavioural approaches [211-215] and neuroimaging approaches [216, 217]. On behavioural level heterogeneous results are reported. Gooding and Tallent [211] and Martin et al. [214] compared the accuracy in a delayed match to sample task with the load of one face. Both found that both healthy controls and patients with schizophrenia performed worse, when the faces had to be matched for emotion compared to identity, but this effect was significantly more present in patients [214]. However, working memory load did not exceed one item, and delay period was rather short in one study [214]. In addition, effects of individual emotions were not analyzed. Linden et al. [212] also used faces displaying different emotions. However, emotions here were an implicit property of stimuli, while faces only had to be matched for identity. Similar to Martin et al. [214] the retention interval was rather short. Both, healthy controls and patients with schizophrenia had increased accuracy for faces with an angry expression, but patients had an overall worse performance. Although patients had the same emotional modulation of memory performance, they performed especially worse when they had to classify angry faces, suggesting that the emotional memory modulation relies on a different brain system than the one associated with working memory performance. Mammarella et al. [213] used emotional words with negative, neutral and positive valence. Sets were formed by a mathematical operation followed by one word. Load varied from two till five sets and participants had to remember the correct order of words, which belonged in one trial always to the same emotional category. Healthy controls and patients with controls recalled the same number of words correctly, for both groups no emotional modulation was found. Patients had more intrusion errors, and intrusion errors were significantly present in trials with positive words, but both effects did not interact. Summarizing the results, there is evidence from experiments that use different emotions as implicit stimulus property, for two independent systems: one that process emotions,

and another processing working memory demands [211-215]. In contrast, experiments that use the emotional expression as an explicit stimulus property, suggest that these systems are less independent, as performance differences in patients in the emotion compared to the identity condition increased significantly more than in healthy controls [211-215].

Studies using FMRI to further disentangle the influence of emotion on cognition found contradictory results, in which probably differences in task design may play an important role. Becerril and Barch [216] report that patients had higher accuracy and decreased response latencies for negative compared to the neutral faces during a N2-back task. At the level of FMRI measurement this finding was associated with increases of BOLD-signal in several regions of the frontal lobe regions, the basal ganglia and bilateral hippocampus in patients. In contrast, healthy controls had increased accuracy for neutral compared to the positive faces. One important aspect of this study is the short ISI of 500ms while stimuli were presented for 2500 ms.

The study of Ursu et al. [217] does not investigate WM in a strict sense, but the ability to rate the emotional meaning of IAPS stimuli after a delay (12 till 22 seconds) typically used in a WM task. The authors suggest that the stimulus has to be held in a buffer and has to be manipulated to rate the picture on three different properties (feeling positive, feeling negative, feeling energized). Patients with schizophrenia significantly more often rated negative stimuli as positive and vice versa. FMRI revealed no differences between healthy controls and patients with schizophrenia during stimulus presentation, but during delay healthy controls displayed significantly higher BOLD-signal compared to patients predominantly in the frontal lobe. The authors suggest that the reduced BOLD-signal reflects the inability of patients to maintain the emotion they have felt during the presentation of the stimulus, leading to the observed mismatch of stimulus rating.

This fits well with the theory [65, 218, 219], which states that patients with schizophrenia are able to experiences emotions similar to healthy controls over short periods, but can not keep them for a longer time period. However, the task did not control, whether subjects had kept the stimulus in mind, thus the mismatch ratings could also be a pure memory disturbance with respect to the stimulus itself and not to the evoked feeling.

In an elegant study, Strauss et al. [215] demonstrated that emotion and cognition influences each other interdependently. A distractor devaluation task was embedded in a working memory task with load of 0 to 2 faces. In the distractor devaluation task, previously attended faces are used to be rated as more trustworthy. WM task load influenced the results of the devaluation task. While in healthy controls the distractor devaluation effect was present at load 1 and 2, in schizophrenia it was only present at load zero, suggesting that higher cognitive demands (increasing load) affects the ability of rating trustworthiness negatively in patients with schizophrenia.

To further evaluate the influence of explicit emotion modulation on working

memory, we used a slightly adapted version of the paradigm earlier tested in the FMRI study of chapter three. Firstly, the question was addressed, whether working memory performance differed between healthy controls and patients with schizophrenia. However, the main question of this experiment was, if there was impairment in WM performance for the emotion condition over and above the general WM impairment, suggesting an interaction between cognitive impairments (WM performances) and emotional disturbances (processing of facial emotional expression) in patients with schizophrenia.

Emotional modulation of attention with an adapted Stroop task

In the seventh chapter we investigated emotional modulation of attention in a group of patients with recent onset schizophrenia compared to a group of healthy controls. on an emotional Stroop Task. The classic Stroop Task investigates the impact of congruent (letters are in the same colour as colour word: RED in red letters) or incongruent (letters are in a different colour as colour word: RED in green letters). Typically, participants react slower to incongruent colour words. Besides colour words, words with positive, negative and neutral content are presented to the participants in the emotional Stroop Task. In several psychiatric disorders it has been shown that the Stroop effect for emotional words is stronger in patients than in healthy controls. We aimed to investigate whether patients with schizophrenia show differences in emotion modulated attention compared to the healthy controls.

Several studies investigated the influence of emotion on attention. Suslow et al. [220] investigated the influence of emotional expression of schematic faces in a visual search task within three different groups of patients with schizophrenia (anhedonic, with flat affect, neither anhedonic no flat affect) and a group of healthy controls. Although the patient groups had increased response latencies, all groups showed an advantage for negative schematic faces, demonstrating the same modulation of attention by emotion in all participants. In a study with an extended oddball paradigm [221] neutral and negative valenced stimuli from the IAPS [36] were presented as novel/distractor stimuli. Patients with schizophrenia were as accurate in the detection of targets and the two categories of novel stimuli as healthy controls, and no valence by group interaction was found, demonstrating similar emotion effects for both groups. With respect to response latencies, the patient group gave slower responses, but again, no group by valence interaction was found. Parks et al [222, 223] examined, whether emotional faces (used as background) would affect sustained attention during a numerical continuous performing test. In both studies number were presented for a short time span at the nose-top of faces with different emotional expressions [222] or on happy face only compared to a blank grey background [223]. Patients with schizophrenia had decreased accuracy and increased response latency for all different emotional backgrounds [222]. Accuracy decreased significantly for stimuli presented on happy faces compared to neutral or sad faces for all participants, and there was no

interaction between group by emotion by block. Separate analysis for both groups revealed that the group of patients with schizophrenia drove the effect for happy faces. Happy faces distracted patients more than a blank grey background when numbers were presented with low luminance as accuracy decreased in this condition significantly [223]. Healthy controls performed equally in both conditions. However, accuracy differences between the different backgrounds disappeared in the patient group, when the luminance of the number stimulus was increased. The results do not support a differential modulation of attention by emotion in patients with schizophrenia. The reduced accuracy for the low luminance stimulus could be mainly an effect of either complexity of the background or a consequence of the smaller contrast between facial background and the low luminance stimulus, an explanation supported by findings from several studies [197, 204], which found impairments in contrast detection.

Another way to investigate emotional modulation of attention is the emotional Stroop Task, which was used in our study presented in chapter 7. Several studies used the emotional Stroop task either in deluded patients with depressed and healthy controls as comparison [224, 225] or in patients with schizophrenia compared to healthy controls only. [226-228]. Study results were heterogeneous, partially due to differences in task design. The two early studies Bentall, Kaney, 1989; Kinderman, 1994) used the card version, while the more recent [226-228] one used computerized single trial versions, in which word categories are presented intermixed. For the standard Stroop task is has been shown that in the card version patients with schizophrenia show a robustly increased Stroop effect compared to healthy controls [229]. In the computerized single trial version, this difference is less prominent or even absent [229]. However, also the studies using the card version [224, 225] revealed different effects of emotional stimuli.

Besides the use of the card version, another important aspect of both studies was that emotional words were either threat-related [224] or personally descriptive adjectives with negative or positive content [225], thus content of emotional words was strongly related to psychopathology of participants. Threat-related stimuli caused significantly higher interference in patients with delusions than both depressed patients and healthy controls [224]. In contrast, personally descriptive adjectives caused significantly higher interference in for both patients groups (delusional disorder or depressed patients) compared to healthy controls [225], independently whether the stimulus was positive or negative. Although patients with delusion showed the highest interference effects, again this was true for both positive and negative adjectives.

In contrast, studies using a single trial version of the Strop task [226, 228] used stimuli, which are chosen from greater data-sets validated in healthy controls. Therefore, the relation with individual psychopathology was not as strong as in the studies discussed in the previous paragraph [224, 225]. Again, contradictory results were obtained. First of all, both studies found no differences with respect to interference or facilitation between patients with schizophrenia and healthy

controls. One even found no differences between the two groups in absolute reaction times [228], a very unusual result, given that increased reaction times in patients with schizophrenia compared to healthy controls is one of the most robust findings in the literature. Effects of interference differed between studies. Demily et al. [226] reported interference for both, positive and negative words, but Philips et al. [228] reported interference for negative, but facilitation for positive words.

We used an emotional Stroop Task to further examine emotional modulation of attention. The classic Stroop Task investigates the impact of congruent (letters are in the same colour as colour word: RED in red letters) or incongruent (letters are in a different colour as colour word: RED in green letters). Typically, participants react slower to incongruent colour words. Besides colour words, words with positive, negative and neutral content are presented to the participants in the emotional Stroop Task. In several psychiatric disorders it has been shown that the Stroop effect for emotional words is stronger in patients than in healthy controls. We aimed to investigate whether patients with schizophrenia show differences in emotion modulated attention compared to the healthy controls.

Social cognition and the Simon task

In the eighth chapter, the last aspect of this thesis is covered: social cognition in patients with schizophrenia For that purpose an adapted Simon task was used to examine the influence of social information on the behaviour of patients with recent onset schizophrenia and healthy controls

One facet of social cognition, emotion recognition, is already discussed in previous paragraphs. The other facets are social perception, attributional bias and theory of mind. The study described in chapter 8 of this thesis is related to social perception, especially the impact of gaze direction on behaviour, even when gaze direction is a non-relevant stimulus feature. Social cognition has received increased attention in the last decade, amongst others because social cognition is an important factor associated with occupational and functional outcome in schizophrenia [230-234]. Others have found that functional outcome and social cognition are independent factors [235, 236]. Perception of gaze is at the borderline between emotion and social perception. Several studies have shown that the gaze direction of faces may influence the perception of emotion [237, 238] and that this is accompanied by differences in BOLD-signal changes among others in healthy controls [237, 239] as well as patients with schizophrenia [238]. The effect of averted gaze differs between emotions. Fear is rated as more intense [237] and better recognized [238] with averted gaze and anger when gaze is directed to the observer [237, 238] On the other hand gaze is a social signal, which may direct attention to the environment. It has been suggested that the averted gaze in fearful faces may be better recognized and rated as more intense, because this pattern of emotional expression and gaze could direct attention to danger outside the actual focus of vision [237]. Interestingly the relationship between gaze and

emotional expression is also present the other way around. Patients with schizophrenia tended to perceive gaze as directed to them earlier than healthy controls when gaze was stepwise rotated from averted to gaze directed to the observer. This effect increased in both groups when the face displayed a fearful expression. [240]. Furthermore, in patients the tendency to perceive eye contact in ambiguous presentations is negatively associated with socio-emotional functioning. Not only gaze perception, but also gaze-induced attention is influenced by the emotional expression in healthy controls [241]. When presenting two faces with gaze directed in opposite directions simultaneously, faces with fearful expressions reduce response latencies to a peripheral target compared to neutral faces, while happy faces increased response latency compared to neutral faces. But when happy and fearful faces were presented simultaneously, no differences between the two emotional expressions could be detected. However, these results support the hypothesis that averted gaze in fearful faces increase attention to stimuli presented in the periphery of the visual field. In several studies it has been shown that gaze directed to the side in which stimuli appeared in the periphery of the visual field facilitates response latencies although gaze was not predictive [242-244]. When certain faces are consistently looking in the same and other faces in the other direction than the target, it is not surprising that after finishing the task, faces looking in the direction of the target are rated as more trustworthy than the other faces [245]. However, this effect is only present in faces with neutral expression and with even much higher significance in faces with happy expression, but not in faces with angry expression. Thus the formation of relationship between the social information (gaze direction) and the later rating of trustworthiness is modulated by the emotional expression of faces, even when participants differentiated faces with gaze directed to target and away from target at chance level. Thus, there is evidence from different sources that gaze influences behaviour at different levels.

Perception of gaze [240, 246-249] and its influence on attentional processes [250-253] has been investigated in patients with schizophrenia. The results of these studies give evidence that the perception of gaze is unaffected in patients with schizophrenia. However, brain processes seem to differ, as patients have a different pattern of BOLD-signal compared to healthy controls, when observing gaze [249]. With respect to the influence of gaze on attention, heterogeneous results are obtained in patients with schizophrenia. Inhibition of return (IOR) describes the observation that a cue spatially corresponding to a subsequent stimulus facilitates reaction time to the target stimulus only if the interval between cue and stimulus is relatively short (<300 ms). Three studies have investigated this phenomenon in patients with schizophrenia [251-253], all found that IOR is disturbed using gaze as cue in patients with schizophrenia, but two also found that IOR is disturbed when geometrical stimuli were used [251, 252]. Thus, the specificity of disturbance of gaze cueing remains doubtfully. In a non-predictive, spatially cued, target detection task, patients with schizophrenia had a response

latency benefit when arrows or eye-like stimuli were used as spatial cues [250]. Healthy controls and patients differed on trend level for eye-like stimuli, but had similar results for arrows as cues, suggesting that the social signal gaze is of less influence in the patient group. Despite the fact that gaze was not predictive in this task, gaze had a relationship with the relevant task feature, attention to a peripherally presented stimulus. In contrast, the gaze induced spatial coding, which we investigated in our study, differs in that aspect from the previous mentioned study. Gaze was a task-irrelevant task property, as participants only had to react to the colour of the stimulus, but not to a spatial cued stimulus. As it has been demonstrated earlier by Zorzi et al. [254] gaze direction influences response latencies in healthy controls, thus when participants are asked to react with one hand to colour A, gaze directed to the hand decreases and gaze directed away from the hand increases response latencies. This difference in response latency is called the Simon effect [255]. Thus, there is evidence that perception of gaze is more or less processed unconsciously, when it is not predictive or even more when it is a task irrelevant stimulus property.
We used an adapted Simon task [254] to examine the influence of social information on the behaviour of patients with schizophrenia and healthy controls. In the classical Simon Task, the influence of the irrelevant spatial property of a stimulus on a lateralized response is examined. In the present experiment stimuli resembling eyes, directing gaze either to the left or right of to the participant were compared to abstract stimuli. Gaze is an essential emotional and social signal, which for example may be misinterpreted by patients with psychosis. We aimed to investigate whether patients with schizophrenia are able to use a gaze to guide behaviour in the same way as healthy controls, thus to what extent gaze as social and emotional stimulus could influence the performance on the cognitive task.

In the ninth chapter the results of the individual studies are discussed in a broader framework and a general conclusion and further research directions are presented.

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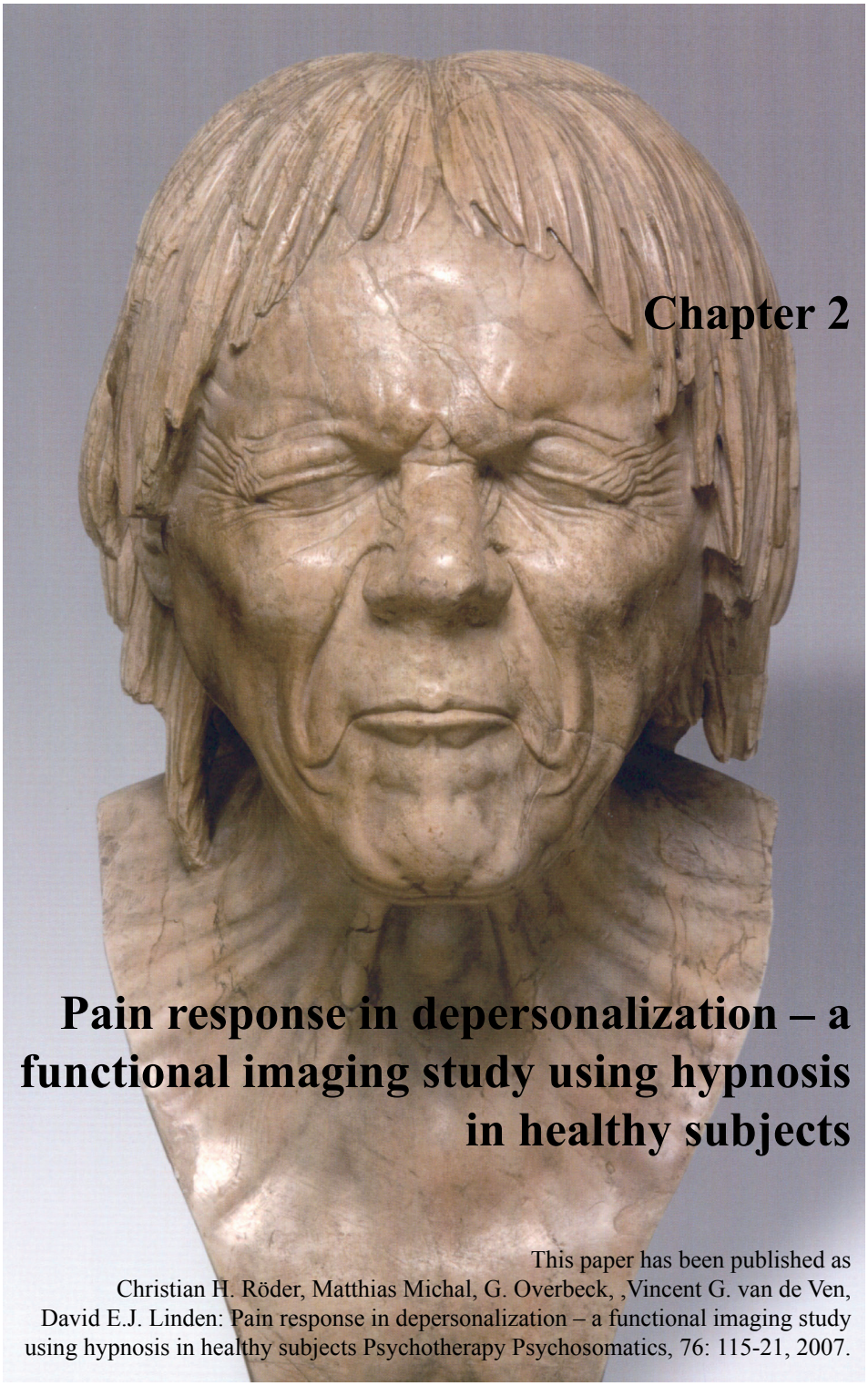

Chapter 2

Pain response in depersonalization – a functional imaging study using hypnosis in healthy subjects

This paper has been published as
Christian H. Röder, Matthias Michal, G. Overbeck, ,Vincent G. van de Ven, David E.J. Linden: Pain response in depersonalization – a functional imaging study using hypnosis in healthy subjects Psychotherapy Psychosomatics, 76: 115-21, 2007.

Abstract

Depersonalization is characterised by persistent or recurrent episodes of detachment from one's self with reduced pain-perception being a common feature Alterations in the body schema similar to the cortico-limbic-disconnection syndrome of pain asymbolia are suggested to be responsible for depersonalization. In this study we used hypnosis to induce depersonalization in healthy subjects and to examine neural patterns of pain perception in the state of depersonalization by means of functional magnetic resonance imaging (fMRI). Pain perception was investigated in 7 healthy subjects with high susceptibility to hypnosis in three different mental states: waking state, hypnotic relaxation and hypnotic depersonalization. Pain was induced with electrical stimulation to the median nerve at the right wrist. FMRI measurements were performed during all states. Nociceptive stimuli led to an activation of the pain-network including somatosensory and insular regions and the cerebellum. Activation was markedly reduced in somatosensory, parietal (BA 40) and prefrontal cortex (BA 9), putamen and the ipsilateral amygdala during hypnotic depersonalization. Subjects reported a significant decrease of pain intensity from waking state to hypnotic depersonalization. Pain response during hypnotic depersonalization was reduced in sensory and affective pain-related areas, reflecting the diminished intensity of the perceived pain. Moreover, a network of cortical and subcortical areas that have been implicated in the perception of the own body was less responsive during depersonalization, which might point to a specific neural mechanism underlying the "out of body" experience. Allthough the small number of subjects does not allow a generalisation of our findings, hypnotic depersonalization seems to be a promising tool for the investigation of psychological and biological mechanisms of self-inflicted injuries as well as the mind-body interplay within the realm of psychosomatic disorders.

In parts the study was supported by the fund of the "Heinrich und Fritz Riese Stiftung 2004".

Introduction

Patients with self-inflicted injuries often report depersonalization, a feeling of detachment from their own body, and no or reduced pain-experience while injuring themselves [1]. Both psychological and somatic factors have been implicated in depersonalization [2] and it has been suggested that depersonalization is produced by a preformed functional brain response that can be triggered under diverse conditions [3]. Although depersonalization is a very common phenomenon [4, 5], clinical and neurobiological research into its mechanisms has started only recently [6].

Neurobiological models of depersonalization focus on alterations of emotional processing [7, 8] and body scheme [9]. Self-reports of patients with pain-asymbolia, where sensory properties of nociceptive stimuli are preserved without an adequate motor or emotional response, show striking similarities with those of depersonalization subjects [8]. Pain-asymbolia has been associated with lesions of the insula, supramarginal gyrus and cingulate gyrus (GC), and cortico-limbic disconnection seems to play an important role [8, 10, 11]. Multisensory integration deficits in the temporoparietal junction [12] have been implicated as neural mechanisms of both depersonalization and out-of-body-experience. These findings are of particular interest in the light of psychoanalytical theories that explain depersonalization as a withdrawal of emotional attachment from the own body [13].

Evidence about the neural origin of depersonalization has come from studies in patients with brain lesions or epilepsy. For the investigation with functional imaging, however, we will ideally use a manipulation that allows controlling the onset and duration of depersonalization. Hypnosis fulfils these criteria because it entails a powerful attentional manipulation [14], leading to changes in perception of external stimuli and one's own body. Previous neuroimaging studies investigated hypnotic compared to dissociative paralysis [15], delusions of alien control [16], hypnotic analgesia [17-20], and hypnotic pain induction [21].

The neurophysiological investigation of both depersonalization and hypnosis has thus started fairly recently, but knowledge of the neural processing of pain relies on a long tradition of research [22]. Electrophysiological and imaging studies have implicated primary (S I) and secondary (S II) somatosensory cortex, thalamus [23], insula, cingulate gyrus (GC) [22] cerebellum [24], putamen [25-27], amygdala [28] and motor cortex (M1) [29] in the pain response.

Here we investigated changes in pain perception and corresponding brain activation during different hypnotic states using fMRI. In contrast to studies examining the effect of hypnotic suggestions intended directly to modulate the experience of pain [18-20], our study aimed at illuminating the neural pattern associated with pain perception during hypnotic depersonalization.

Methods

Subjects

Seven healthy subjects (mean age 26 years, range 22-34, 5 fem./ 2 mal.) with a score higher than 8 on the Harvard Scale of Hypnotic Susceptibility (HGSHS-A) [30] and responsiveness on our induction method of depersonalization participated. Mean score of HGSHS-A was 9.2 (SD 1.0, range 8-10). All subjects gave informed consent and were in normal ranges of the Symptom-Check-List-90-R [31] and the Cambridge Depersonalization Scale [32]. Standard exclusion criteria for fMRI research were used. The protocol was approved by the local ethics committee and in accordance with the Declaration of Helsinki 1975.

Pain stimulus

Pain stimulation was delivered with an MR-compatible device (Nicolet Medican) for measurement of somatosensory evoked potentials over median nerve of the right wrist. Stimulus location and motor threshold were defined as the point where a muscle contraction of the adductor pollicis brevis muscle could be elicited with the weakest possible current. Individual pain tolerance was determined as maximum intensity of current tolerated for at least 15 seconds and expressed in percent of maximum current. Differences between thresholds of motor actication and pain tolerance were at least 25%. Stimuli were DC square pulses with duration of 100 ms and frequency of 6.1 Hz. We opted for median nerve stimulation in order to obtain an objective measure (motor response), which ensured correct stimulus application and location in all mental states via motor threshold determination.

Hypnosis protocol

Brain activation was examined during two different states of hypnotic trance, hypnotic relaxation and hypnotic depersonalization, and one waking state control condition. Waking state was defined as lying quietly with eyes closed. Hypnosis was induced via a standard fixation method while subjects were lying in the scanner and the two hypnotic trance conditions were evoked as described below.
Hypnotic relaxation: To achieve a state of hypnotic relaxation, we applied a standard suggestion in hypnotic pain treatment [33] of leaving the unpleasant and painful presence and repairing to a place in the fantasy or memory, where one feels comfortable.
Hypnotic depersonalization: A suggestion was modelled after the clinical experience with depersonalized patients and phenomenological and theoretical descriptions [13, 34]. It aimed at the detachment of the self from the body. Subjects were further encouraged to see their body from outside like in autoscopy. We validated our induction method via subjects' self-reports.

Scanning procedure

The scanning procedure comprised three separate sessions for waking state, hypnotic relaxation and hypnotic depersonalization each.

Median nerve stimulation was applied as described above (pain stimulus) via a shielded port when subjects were lying in the MR-scanner. Three different protocols with different interstimulus intervals, each comprising nine periods of stimulation at the individual pain threshold were applied. Each stimulation period lasted 12.4 seconds and was separated from the next by a stimulation-free interval (baseline) ranging between 12.4 and 21.7 seconds.

After scanning, subjects were asked to rate their experience of stimuli during the hypnotic relaxation and the hypnotic depersonalization session in percent intensity change from the waking state session set as 100%. This approach was chosen to achieve a level of interindividual homogeneity. Moreover subjects rated the intensity of their experience of relaxation during hypnotic relaxation and of detachment during hypnotic depersonalization with a visual analogue scale ranging from 0 (not at all as) through 100% (highest) after the scanning session. Because of possible residual effects of hypnosis and pain-modulation suggestions, the waking state condition was always presented first, followed by the hypnotic relaxation and then the hypnotic depersonalization condition, following the procedure of Hofbauer [18].

Image acquisition

FMRI was performed on a 1.5 T Magnetom Vision MRI scanner (Siemens, Erlangen, Germany) equipped with a standard head coil and an actively shielded gradient coil (25mT/m). Data covering the entire brain were acquired using a gradient echo EPI sequence (1 volume = 19 axial slices, TR = 3100ms, TE = 60 ms, Flip angle 90°, FoV = 240 x 240 mm2, matrix 64 x 64, voxel size = 3.75 x 3.75 x 5 mm3). Each scan comprised 181 volumes (543 s per run). A T1 weighted 3D MPRage scan (magnetization-prepared rapid acquisition gradient echo, TR = 9.7 ms, TE = 4ms, FA 12°, Matrix 256 x 256, FOV 256 x 256 mm2, voxel size 1.0 x 1.0 x 1.0 mm3) was recorded in every session for anatomical coregistration.

Data analysis

Measures of ratings and questionnaires were calculated with SPSS 11.5.1. FMRI-data were analysed with Brain Voyager 4.9. Functional data were preprocessed as follows: (1) all slices within a volume were corrected for relative temporal shift, (2) the complete set of functional data (three functional runs) of each subject were transformed into Talairach space [35], yielding a 4D data representation (volume time course: 3 space, 1 time), (3) the first volume of each time-series was used as a reference volume for a 3D motion correction algorithm, (4) EPI images were spatially smoothed using a Gaussian kernel with a full width at half maximum (FWHM) of 8 mm and (5) for temporal filtering each voxel's time course was convolved with a Gaussian kernel with a FWHM of 2. Linear drifts of the

signal with respect to time were removed from each pixel's time course.
Statistical analysis was based on the application of the multiple regression analysis to time-series of task-related functional activation [36] implemented in the software package [37]. The general linear model (GLM) was applied to the z-normalized volume time-courses of every session. Z-normalization of the BOLD signal was performed subject by subject for each voxel time course. The signal values during application of stimuli at individual pain-threshold in each condition were considered as effects of interest. Corresponding predictors were obtained by fitting a linear model of the hemodynamic response to the time courses during which the different stimulus classes were presented.
To analyze the effects of the single conditions, 3D group statistical maps were generated. To this end, F values and the beta values associated with a specific set of predictors were calculated for each voxel on the basis of the least mean squares solution of the GLM. Resulting P values were corrected for multiple comparisons using a Bonferroni adjustment. Statistical group maps are based on a fixed effects analysis and thus pertain only to the subjects investigated in this study.
We calculated contrast-maps comparing baseline and painful stimulation for each condition (waking state, hypnotic relaxation, hypnotic depersonalization) separately in order to identify the pain response in each condition. Changes of the pain response during hypnosis were assessed by calculating t-maps between the conditions waking state > hypnotic relaxation, waking state > hypnotic depersonalization and hypnotic relaxation>hypnotic depersonalization.

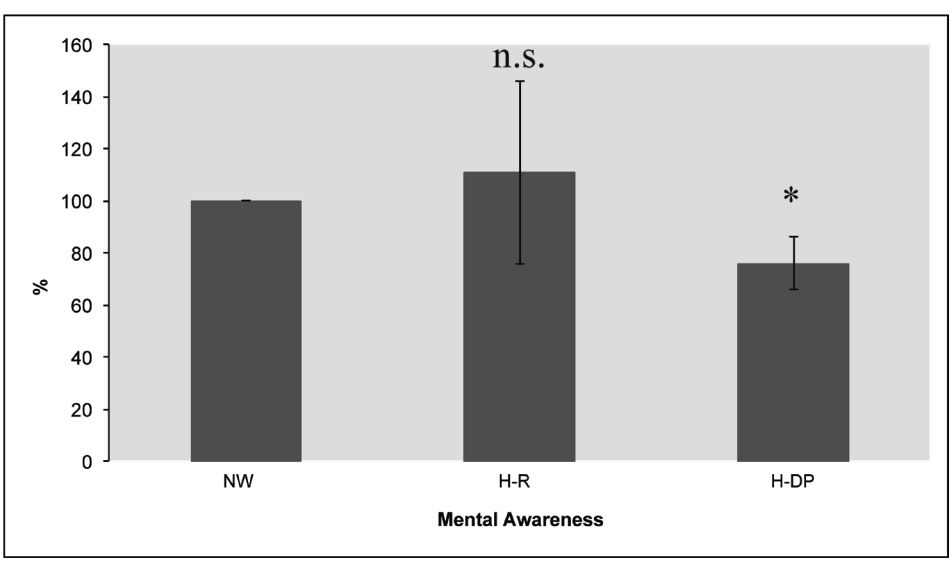

Fig 1. Intensity ratings of pain experience from all subjects (n = 7). * p = 0.017.

Results

Subjective reports

Perception of pain intensity was unchanged during hypnotic relaxation (mean 110.7, SD 35.2, Wilcoxon-Test, Z = 0.530, n.s.) but significantly reduced during hypnotic depersonalization (mean 76, SD 10.34; Z = 2.384, p =0.017; effect size d=2.3) compared to waking state (Fig. 3). Intensity of hypnotic depersonalization was rated as 67.1±19.6 (range 30–90%) and intensity of the hypnotic relaxation as 80.7±8.4 (range 65-90%) by the subjects. After scanning, self-reports of subjects were recorded and evaluated for their consistency with experiences of depersonalization.

fMRI results

Stimulation at individual pain threshold as determined before hypnosis activated the contralateral primary (cSI) and bilateral secondary somatosensory cortex (cSII, iSII), bilateral insula (cIns, iIns), cingulate gyrus (GC), and the ipsilateral cerebellum in session waking state at significance level of p(corr)< .0001. While in the hypnotic relaxation-condition some regions revealed an increase

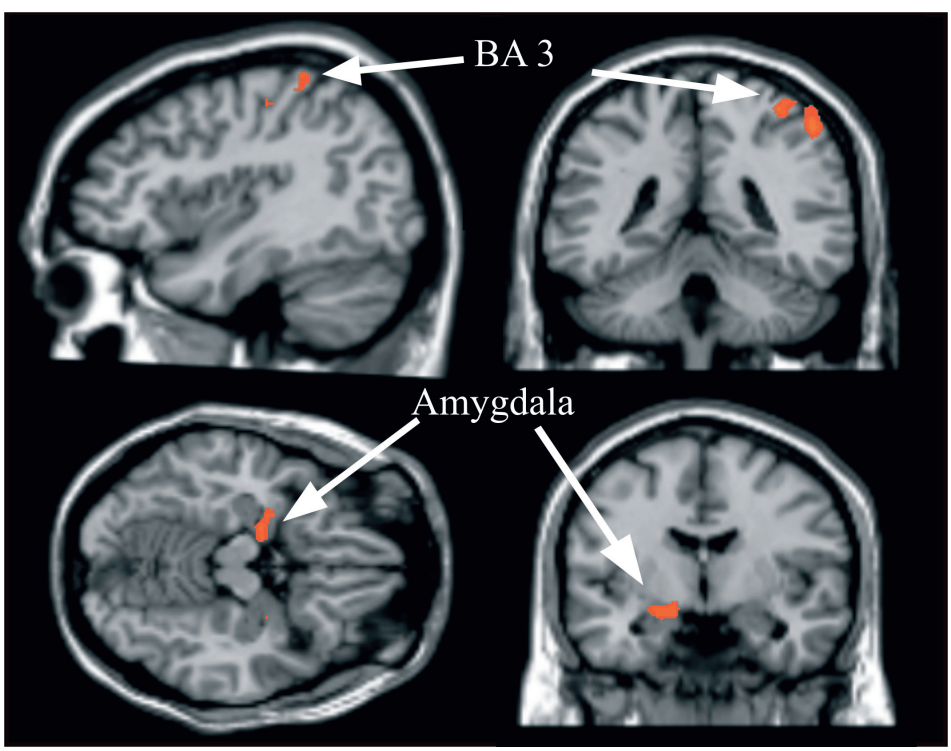

Fig. 2. Contrast map of differences between the waking state (N-W) and hypnotic depersonaliza-tion (H-DP),showing areas of signifi cantly reduced activity during H-DP in the left (contralateral to stimulation) somatosensorycortex (BA3) (upper row) and the right amygdala (lower row).

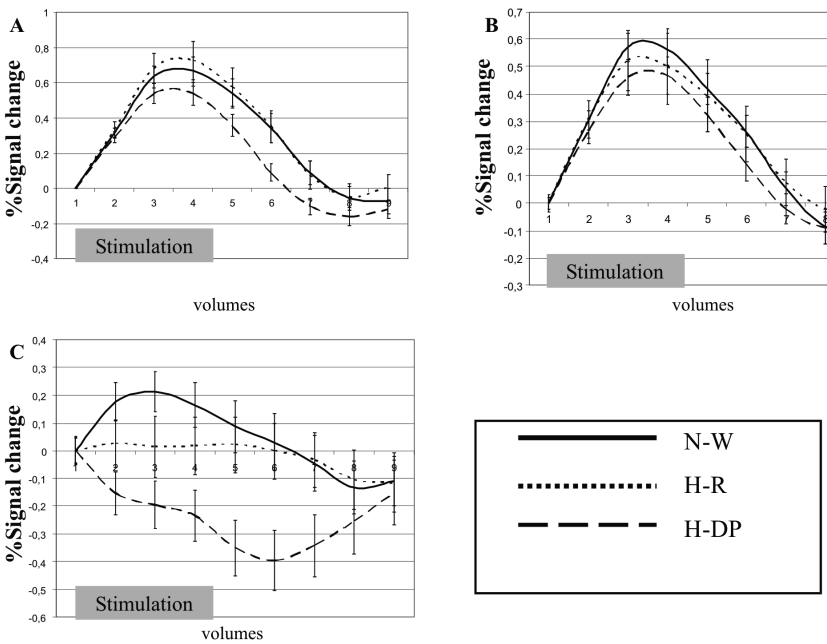

Fig. 3 Time courses of regions of interest for all three conditions. Somatosensory cortex (BA3). b Temporoparietaljunction (BA40). c Amygdala.

in the number of activated voxels, there was an overall decline in the hypnotic depersonalization-session compared to the waking state-condition. Comparison between the waking state > hypnotic depersonalization showed at a threshold of p <0.005 (corr.) a decrease of activation (Fig.2) in the cSI (BA3), cSII(BA40), contralateral putamen and ipsilateral amygdala during hypnotic depersonalization. The contrast hypnotic relaxation > hypnotic depersonalization showed activation in the contralateral postcentral cortex (BA 3 und BA5), cSII (BA 40), CG (BA 24) and the ipsilateral insular (BA 13) Time courses of activations in ipsilateral BA3, BA 40 and the contralateral amygdala in each condition are displayed in Figure 3.

Discussion

We assessed effects of hypnotic depersonalization on pain perception and its neural correlates in healthy subjects. Subjects' reports after scanning revealed that depersonalization was induced successfully. hypnotic depersonalization, but not hypnotic relaxation, strongly attenuated experience of pain. A reason for absence of pain reduction during hypnotic relaxation might be that suggestions in this condition might have biased subjects to focusing their attention on their bodies, which was not the case in the hypnotic depersonalization condition. FMRI data matched the direction of hypnosis-induced changes of subjective reports. Pain stimulation before hypnosis activated the central pain network [22, 24], and sev-

Table 1. Talairach coordinates, voxel numbers (NoV) of ROI-analysis for activated clusters. BA: Broca area

	Increased activity					
	Region	Hemsp.	x	y	z	voxel
Waking state	Postcentral Gyrus, BA 3	L	-33	-35	57	28895
	Cingulate Gyrus, BA 24		0	-4	-46	15728
	Temporal Lobe & Insula BA 29	L	-46	-24	16	12226
	Inferior Parietal Lobule, BA 40	R	53	-27	26	8370
	Insula, BA 13	L	-44	-2	9	5979
	Insula, BA 13	R	44	8	9	22675
	Cerebellum, Anterior Lobe	L	-25	-59	-26	5995
	Cerebellum, Anterior Lobe	R	15	-53	-20	28176
Hypnotic	Postcentral Gyrus, BA 3	L	-32	-33	55	25915
Relaxation	Cingulate Gyrus, BA 24	L	-3	-5	44	9609
	Temporal Lobe & Insula BA 29	L	44	-25	16	11511
	Inferior Parietal Lobule, BA 40	R	52	-30	24	7969
	Insula, BA 13	L	-42	0	7	10528
	Insula, BA 13	R	42	9	10	16949
	Cerebellum, Anterior Lobe	R	10	-54	-20	14440
Hypnotic	Postcentral Gyrus, BA 3	L	-34	-31	56	17836
Depersonal.	Cingulate Gyrus, BA 24	L	-3	-9	48	1706
	Temporal Lobe & Insula BA 29	L	-46	-25	15	11369
	Inferior Parietal Lobule, BA 40	R	52	-27	23	5412
	Insula, BA 13	L	-46	-1	9	8573
	Insula, BA 13	R	45	7	11	16698
	Cerebellum, Anterior Lobe	R	9	-55	-17	6921
	Decreased activity					
Waking state	Postcentral Gyrus, BA 3	R	21	-35	61	9890
Hypnotic Relaxation	Postcentral Gyrus, BA 3	R	39	-30	57	5595
Hypnotic	Postcentral Gyrus, BA 3	R	34	-33	55	2825
Depersonal.	Medial Prefrontal Gyrus, BA 9	L	-5	53	14	1675
	Medial Prefrontal Gyrus, BA 9	R	5	54	15	1586

Table 2. Talairach coordinates, voxel numbers (NoV) of ROI-analysis for activated clusters for the different contrasts. BA: Broca area

	Region	Hemsp.	x	y	z	voxel
Waking state	Precentral Gyrus, BA 4	L	-29	-24	64	1130
> Hypnotic	Parietal Lobe, BA 40	L	-49	-30	46	3002
Relaxation						
Hypnotic	Precentral Gyrus, BA 4	R	11	-31	64	3594
Relaxation						
> Waking state						
Waking state	Postcentral Gyrus, BA 3	L	-34	-33	58	82
> Hypnotic	Precentral Gyrus, BA 4	L	-27	-22	62	1628
Depersonal	Parietal Lobe, BA 40	L	-48	-34	48	506
	Amygdala	R	22	-30	24	600
	Putamen	L	-25	0	-1	890
Hypnotic	No Activation					
Depersonal.						
> Waking state						
Hypnotic	Postcentral Gyrus, BA 3	L	-16	-37	67	426
Relaxation	Postcentral Gyrus, BA 3	L	-28	-42	64	733
> Hypnotic	Parietal Lobe, BA 40	L	-48	-36	49	176
Depersonal	Cingulate Gyrus, BA 24	L	-5	9	30	86
	Insula	R	44	13	-2	114
Hypnotic	No Activation					
Relaxation						
>Hypnotic						
Depersonal.						

eral of these regions showed a substantial decrease in their response in the hypnotic depersonalization condition. The contrast waking state > hypnotic depersonalization revealed significant reduction of activation in SI, contralateral motor cortex, parietal lobe (BA 40), putamen and the ipsilateral amygdala. A reduction of SI activity had also been observed under suggestions concerning intensity of pain perception [18] but only when suggestions of high and low intensity were contrasted. The reduction of SI activity by hypnotic depersonalization when compared to waking state is thus a novel finding of the present study. The absence of activity reduction in cSI in the contrast waking state > hypnotic relaxation is in keeping with a recent study [20] on thermal pain stimulation during hypnotic

relaxation.. In further extension of previous studies, we found an activation difference in Brodmann area (BA) 40, where lesions have been found to result in the disconnection syndrome underlying pain asymbolia [10, 11]. Moreover area BA 40 is generally suggested to be involved in mental body representation [12, 38] and self-referential processing [39]. Reduced activity in BA 40 during hypnotic depersonalization in contrast with waking state and hypnotic relaxation can thus be interpreted as leading to a reduced awareness of the body and to the subjective state of being "out-of-one-own's-body".

Reduced activation during depersonalization was also observed in the amygdala [40, 41]. Neuroanatomical studies [42] showed reciprocal connections between the rat amygdaloid complex and cortical areas. We therefore interpret reduced activity in the amygdala, which is related to the reduced affective dimension of pain during depersonalization, as secondary to the reduced activation of the pain network. It is unlikely that this reduced amygdala response was merely an effect of habituation because our stimulation paradigm included a time gap of approximately 30 min between waking state and hypnotic depersonalization, whereas the amygdala habituation described with passive viewing of emotional faces [43-45] arose rapidly within one scanning session.

The role of the basal ganglia in pain perception and avoidance behaviour [46, 47] has long been documented in animal research, but has only recently been addressed in human neuroimaging studies. Lesion data [27] demonstrate reduced pain perception in the contralateral limb after putaminal hemorrhage. FMRI studies reported involvement of the basal ganglia in pain perception [25] and activity changes during painful stimulation in hypnosis [20]. We therefore interpret the reduced putamen activation in our study as a result of reduced motor withdrawal behavior to pain stimuli during hypnotic depersonalization.

We furthermore detected reduced activity in ipsilateral medial prefrontal cortex (BA9). Similar changes were described in a recent study using hypnotic relaxation [20] but not in earlier studies using pain related suggestion [18, 19]. BA9 has been implicated in attention to and anticipation of pain [48], and its reduced activity during hypnotic depersonalization might reflect reduced subjective awareness of pain stimulation. Further studies using different suggestions may lead to a more substantial understanding of the role of prefrontal cortex during hypnosis.

Important limitations of the present study include the small number of subjects and general difficulties of inducing and monitoring hypnosis in the MR environment [19]. The fixed-effect analysis of the fMRI data allows no extension of our findings to hypnosis in general. However, based on the subjects' reports and reduced pain experience we are confident that our hypnosis protocol was successful.

This report shows that altered mental states, which influence the experience of pain, are accompanied by measurable changes in brain processes. Hypnosis has the unique property to allow for the induction of specific mental states, through appropriate suggestions, over well-defined time periods. It is furthermore a wide-

ly applied tool for clinical psychological intervention in various functional and mental disorders. Thus, future combination of hypnosis and functional imaging may benefit both the neuroscience of consciousness and the investigation of the biological mechanisms of psychotherapy and dissociative disorders.

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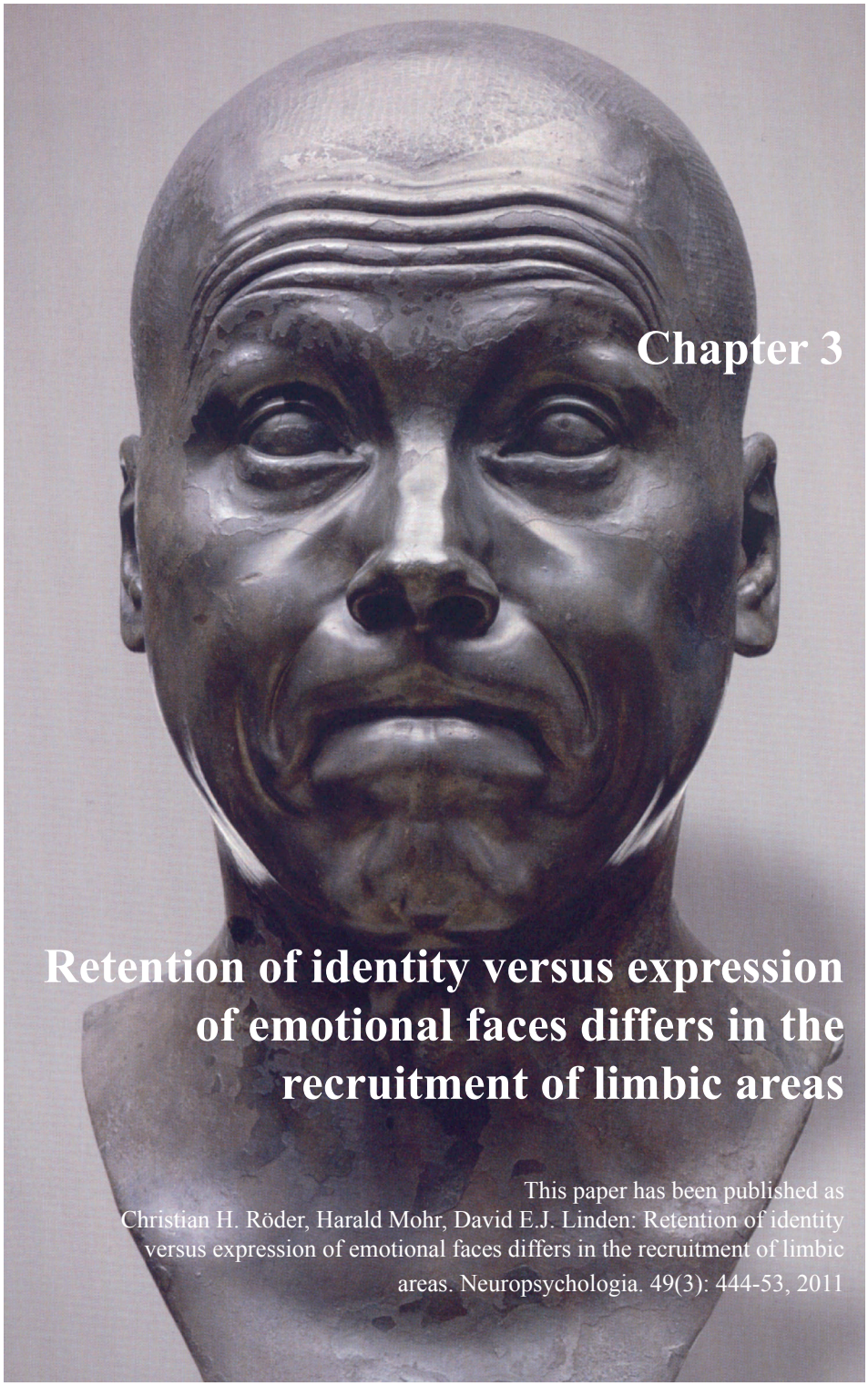

Chapter 3

Retention of identity versus expression of emotional faces differs in the recruitment of limbic areas

This paper has been published as
Christian H. Röder, Harald Mohr, David E.J. Linden: Retention of identity versus expression of emotional faces differs in the recruitment of limbic areas. Neuropsychologia. 49(3): 444-53, 2011

Abstract

Faces are multidimensional stimuli that convey information for complex social and emotional functions. Separate neural systems have been implicated in the recognition of facial identity (mainly extrastriate visual cortex) and emotional expression (limbic areas and the superior temporal sulcus). Working- memory (wm) studies with faces have shown different but partly overlapping activation patterns in comparison to spatial wm in parietal and prefrontal areas. However, little is known about the neural representations of the different facial dimensions duringwm.In the present study 22 subjects performed a face-identity or face-emotion wm task at different load levels during functional magnetic resonance imaging. We found a fronto-parietal-visual wm-network for both tasks during maintenance, including fusiform gyrus. Limbic areas in the amygdala and parahippocampal gyrus demonstrated a stronger acti- vation for the identity than the emotion condition. One explanation for this finding is that the repetitive presentation of faces with different identities but the same emotional expression during the identity-task is responsible for the stronger increase in bold signal in the amygdala. These results raise the question how different emotional expressions are coded in wm. Our findings suggest that emotional expres- sions are recoded in an abstract representation that is supported at the neural level by the canonical fronto-parietal WM network.

Introduction

Functional imaging studies of visual working memory have focused on the maintenance and manipulation of visual objects, features and spatial information [1, 2]. Important areas involved in visual working memory processes are the prefrontal cortex, intraparietal sulcus and higher visual areas. Each of these regions is supposed to subserve a special function in this network. It has been suggested that some areas in the pre- frontal cortex are specialised regarding the material type (object, spatial, verbal) [3-5], while others suggest that differences are mainly based on processes such as maintenance, manipulation, or inhibition, which are necessary to perform the WM task [6, 7] or by an interaction between material type and processes [8].

Faces are multidimensional stimuli and convey many important features simultaneously. They represent a special category in the field of visual objects, probably based on their importance for the recognition of relevant others (identity) and for nonverbal communication (emotional expression). The identity of a person can be recognised by his/her individual physiognomy, which is based on the spatial composition of facial features (nose, eyes, mouth, etc.). Emotional expression is then derived from subtle changes in the spatial composition of facial features [9]. Neuroimaging has elucidated the brain structures involved in the processing of faces [10, 11] and their emotional expression [12-14]. These studies converge to suggest that structures involved in the recognition of the identity of faces (structural and static properties of faces) are mainly located in the extrastriate visual cortex [15, 16]. More changeable configurational features of faces (emotional expression) are processed in the superior temporal lobe [15-17]. Further support for the role of the superior temporal cortex comes from animal studies with single cell recordings [18, 19] Many functional neuroimaging studies have investigated the impact of emotional expression of human faces on brain activity [12, 13, 20-22]. The amygdala is the structure mostly associated with the recognition of emotional expressions [12, 21, 23-25], although the debate is on-going as to whether the amygdala primarily is active to negative facial expressions as fear and sadness or relevant in recognising all human emotional expressions. Breiter et al. [26] found that the repeated presentation of faces with emotional expressions causes a reduction of amygdala activity, but Gläscher et al. [20] found increased amygdala activity for the repeated presentation of fearful faces of different subjects compared to conditions where either identity was constant or emotion was varied. In working memory, faces show partly overlapping activation patterns in comparison to spatial WM [17, 27] with a dorso-ventral gradient for spatial versus facial stimuli [16, 17].

Two recently published studies investigated WM of emotional faces. LoPresti et al. [28] explicitly instructed subjects to match a sample and a test face either for identity or for the emotional expression. In the identity condition, sample and test faces expressed a different emotion, whereas in the emotion condition sample and test faces differed in identity. The authors focused on three structures more

active in the delay for faces versus a control stimulus, the left orbitofrontal cortex (OFC), the left amygdala and the left hippocampus. Only the OFC had significantly higher activity for the emotion task during the presentation of the sample face and significantly higher activity for negative faces during the presentation of the test face. The absence of differences between the two conditions during delay came as a surprise. However, it is important to notice that the authors only measured working memory at a load of one, which may have led to a marginal activation of emotion- or identity specific networks. Jackson et al. [29] used a design wherein emotional expression was varied at four load levels. Subjects were only asked to match the faces for identity, so the emotional aspect was studied implicitly. Another important difference was the short delay of only 1 s, which did not allow for a separation of the processes of encoding, maintenance and retrieval. This study revealed higher activity for negative emotion (angry faces) in the right hemispheric inferior frontal gyrus, superior temporal gyrus and globus pallidus internus for all conditions.

Load-dependent changes are an inherent characteristic of the brain's working memory networks [1]. We therefore regarded the manipulation of the number of faces to be maintained in either the identity or emotion task as crucial. In the

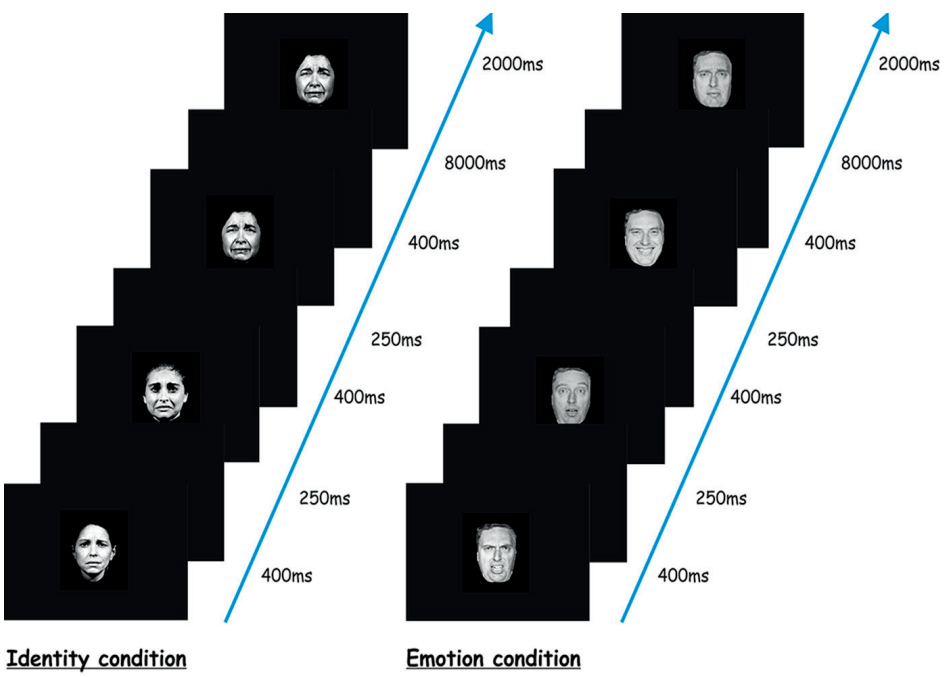

Figure 1: experimental design for load 3. Left: identity condition with 3 females displaying the same emotion. Right: emotion condition with the same male displaing 3 different emotions.

present study we focused on neural processes during the maintenance phase for identity or emotional expression of faces at different load levels. Because of its dual role in emotion processing and memory, we hypothesized that the amygdala and connected limbic areas would play an important role in the maintenance of emotional faces.

Methods

Participants

Twenty-two right-handed volunteers (13 females/9 males) (mean age = 27.3, SD = 4.3) with normal or corrected to normal vision participated in the experiment. The subject's physical health was verified in an interview before the study, and those who had a history of neurological diseases, psychiatric diseases, or drug or alcohol abuse were excluded. No subject was taking medication affecting cerebral blood flow at the time of the study. All participants gave informed consent and experimental procedures were approved by the local ethics committee and in accordance with the Declaration of Helsinki 1975

Stimuli and experimental procedure

In each trial of the paradigm, participants had to memorise one, two, or three sequentially presented black-and-white exemplars human faces taken from the samples of Ekman [30] and Gur et al. [31] in a forced choice paradigm. Faces displayed the following emotions: anger, disgust, fear, happiness, sadness, surprise or a neutral expression. Trials consisted either of the same subject expressing different emotional expressions (emotion condition) or different subjects with the same emotional expression (identity condition), leaving some ambiguity in the case of only one presented stimuli. Faces were cropped with an individually formed shape in order to avoid that peripheral face features allow easy identification of faces. The term emotion was explicitly not named in the instruction to avoid verbalisation of emotional expressions. Stimuli were matched for gender, but not for emotional expressions, due to the fact that there are more negative facial emotional expressions and a limited number of faces. Sample stimuli were presented for 500 ms each. In case of presentation of two or three faces, stimuli were separated by 250 ms blank screens. After a 8 s delay, one exemplar from the same category was presented as test stimulus, and participants had to decide by button press whether it matched one of the sample stimuli (50% matches) (Fig. 1).

Dependent on the number of presented stimuli, trials were separated by an inter-trial interval of 8000, 8750 or 9500 ms. Ninety trials (45 per category) were presented in 3 runs, each containing 30 trials in randomised order. Stimulus presentation was controlled by a personal computer running the Experimental Run Time Software (Berisoft GmbH, Germany). Images were back-projected on the centre of a screen, subtending 5◦ of visual angle, and viewed by participants

through an angled mirror mounted on the head coil. Before the main experiment participants were given a short practice session inside the scanner.

Image acquisition parameters

Anatomical three-dimensional T1-weighted images and functional images were acquired on a 3 T Magnetom Trio scanner (Siemens Medical Systems, Erlangen, Germany) equipped with a standard head coil. A T1 weighted 3D MPRage scan (magnetization-prepared rapid acquisition gradient echo, TR = 9.7 ms, TE = 4 ms, FA 12◦, Matrix 256 × 256, FOV 256 mm × 256 mm, voxel size 1.0 mm × 1.0 mm × 1.0 mm) was recorded in every session for anatomical coregistration. Functional images were collected using 30 slices (3 mm thickness with 3.45 mm × 3.45 mm in-plane resolution) covering the whole brain with a BOLD- sensitive EPI sequence (TR =2 s, TE = 30 ms, FA= 90◦ ; FOV = 220 mm, matrix = 64 × 64; duration of each run = 618 s). To minimize head movements the head was fixed with foam pads that were attached to the holding fixture of the head coil.

Analysis of behavioural data

Behavioural data were analysed with SPSS 15 (SPSS, Inc.). Signal detection models were used to analyse the data. Accuracy was calculated as percentage correct answers per category. Reaction times were calculated for correct answers only. In addition, A-prime (A') scores were calculated as measure of signal detection sensitivity [32] to detect an interference effect. A-prime increases from 0.5 for chance performance to 1 for perfect performance. A-prime was used instead of d-prime because A-prime is more robust against violations of the assumption that the variances of the hypothetical distributions are equal [33] and A-prime does not suffer from the indeterminacy of d- prime that occurs in the absence of false alarms. A-prime estimates the area under the receiver operating curve and was calculated for each participant following the formula by Grier [32]:

$$A' = 0{,}5 + [(H - FA) \times (1 + H - FA)]/[4 \times H \times (1 - FA)]$$

where H (hit) is the correct detection of matching trial and FA (false alarm) is the nonmatching trial identified as matching trial.
If FA > H, the point lies beyond the chance diagonal and the following formula is used:

$$A' = 0{,}5 - [(FA - H) \times (1 + FA - H)]/[4 \times FA \times (1 - H)].$$

Analysis of imaging data

Image analyses were performed with Brainvoyager QX, version 1.10.4 (Brain Innovation, Maastricht, The Netherlands). The first four volumes of each run were automatically discarded due to signal stabilisation. Data pre-processing included slice scan time correction with the first scan time within a volume used as a reference for alignment by sinc-interpolation, three-dimensional motion correction, spatial smoothing with an 8 mm Gaussian kernel (full width at half maximum), temporal high pass filtering with a cut-off of 1/206 s to remove low-frequency non-linear drifts of three or fewer cycles per time course, and linear trend removal. Talairach transformation was performed for the complete set of functional data of each subject, yielding a 4D data representation (volume time course: 3 × space, 1 × time). Statistical analysis was performed by multiple linear regression of the BOLD response time course in each voxel at the individual level. Two of the 22 participants had to be excluded completely, and the data from one run from 3 participants were excluded due to extensive movement artefacts. For each participant, the general linear model included six experimental conditions (identity load 1, 2 and 3; emotion load 1, 2 and 3) and three task phases (encoding, delay and retrieval). The signal values during these phases were considered the effects of interest. The corresponding predictors were obtained by convolution of an ideal box-car response with gamma function model of the hemodynamic response. The encoding phase lasted for 1250 (load 2) to 2000 (load 3) ms and was modelled by a predictor covering the TR after trial onset. Although the delay lasted for 8 s, it was only modelled by its third TR (7–8 s from trial onset). This predictor was thus separated from encoding by 4 s and from the following retrieval predictor (11–12 s) by 2 s. We used this approach following the theoretical framework of Postle [34]. Because of the inertia of the BOLD signal, sequential cognitive operations are difficult to disentangle; therefore each phase (encoding, delay, retrieval) is temporally dependent on the previous one. Based on the previous work of Zarahn et al. [35], Postle [34] proposes that an interval of at least 4 s between two consecutive predictors is necessary to disentangle the effects of a specific predictor without contamination through the previous one. It seems reasonable that carry-over effects from the encoding phase on delay are much stronger, than carry over effects from the delay phase on retrieval, and thus an interval between the delay and retrieval of one TR seemed sufficient. Trials with incorrect answers were modelled with a separate predictor.

This analysis resulted in beta-values for each predictor for each subject (n = 20). Beta-values of the three phases (encoding, delay and retrieval) were entered separately into a random effects ANOVA with the factors load (2 and 3), task (emotion and identity) and phase (encoding, delay, retrieval). Main effects (load, task) and inter- action between the factors were thresholded at $p < 0.005$ (uncorr.) with a minimal cluster size of 10 contiguous voxels. Only the factor load during the encoding phase was thresholded at $p < 0.001$ (uncorr.), because the visual stimulation led to high changes of the BOLD-signal. Reported t- and p-values

represent cluster level analysis. In order to control for any effects of performance differences between tasks we also performed an analysis of covariance (ANCOVA) with the factors task and load, adding the difference of A' - values between tasks for each participant as covariate.

Table 1: Behavioural data of task performance

	ID Load 2	**ID Load 3**	**EMO Load 2**	**EMO Load 3**
Accuracy	0.81 (0.13)*	0.72 (0.13)	0.76 (0.11)	0.72 (0.14)
A-prime	0.88 (0.08)	0.81 (0.14)	0.83(0.08)	0.78 (0.13)
Hit rate	0.79 (0.12)	0.71 (0.14)	0.75 (0.11)	0.71 (0.14)
False alarm	0.17 (0.1)	0.23 (0.13)	0.21 (0.08)	0.25 (0.12)
RT (ms)	1094 (149)	1162 (163)	1096 (173)	1170 (150)

*mean values, standard deviation in brackets.

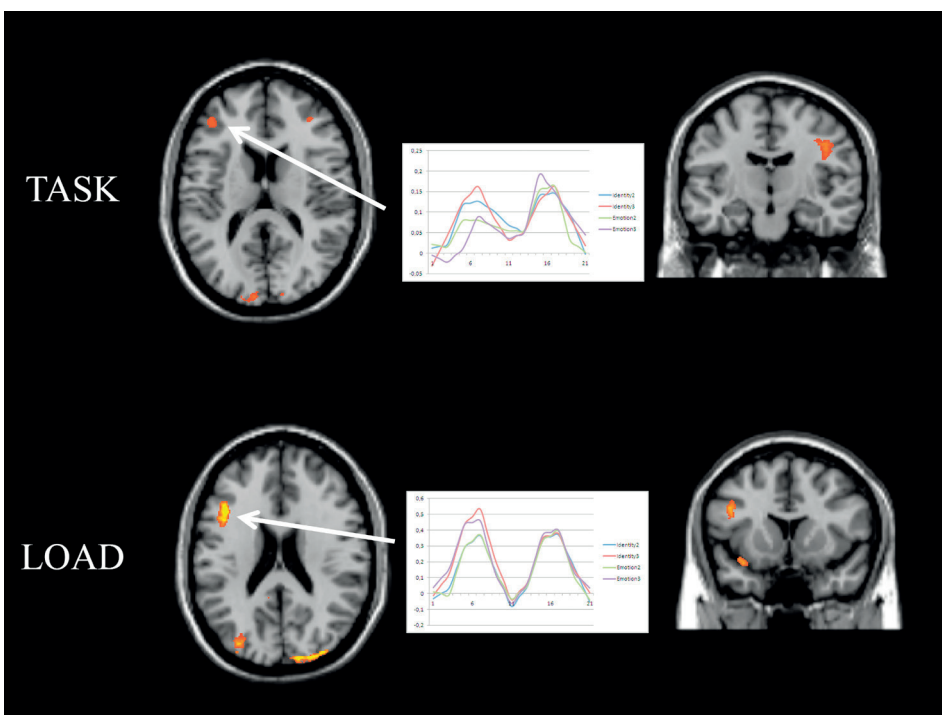

Fig. 2. Axial and coronal slide of the task and load contrast for encoding. In the middle time courses of BOLD signal for the designated clusters (time resolution in seconds). For details of clusters with increased BOLD-signal see text and Table 2.

Table 2: Brain regions exhebiting significant activity of two-way interactions from ANOVA during encoding. X, Y and Z represent coordinates in the Talairach space. t- and p- values are derived from region-of-interest analysis.

LOAD			**Whole Brain p<.001**		**Load 3 > Load 2**	
x	**y**	**z**	**voxel**	**Region**	**t-Value**	**P-value**
-1	17	47	150	Medial frontal gyrus, BA6	4.166	0.000524
25	-70	43	301	Superior parietal lobe, BA7	4.394	0.000312
10	-81	40	1537	Precuneus, BA7	2.848	0.010294
-17	-83	35	1121	Cuneus, BA19	2.742	0.012948
46	-39	38	514	Inferior parietal lobe, BA40	5.048	0.000071
43	13	26	1713	Middle frontal gyrus, BA9	4.828	0.000117
43	-74	1	1548	Inferior occipital gyrus, BA19	5.895	0.000011
-14	-67	-8	3258	Lingual gyrus, BA18	5.537	0.000024
-10	-60	-6	2916	Lingual gyrus, BA18	6.557	0.000003
-32	-81	-3	521	Inferior occipital gyrus, BA18	4.684	0.000162
39	-44	-18	495	Fusiform gyrus, BA37	4.451	0.000274
TASK			**Whole Brain p<.005**		**Identity > Emotion**	
x	**y**	**z**	**voxel**	**region**	**t-Value**	**p-Value**
-1	-54	58	19	Precuneus, BA7	3.374	0.003185
36	-59	51	187	Superior parietal Lobule, BA7	3.069	0.006316
7	-67	50	163	Precuneus, BA7	3.521	0.002283
4	-59	40	261	precuneus, BA7	4	0,000767
-36	-15	38	670	Precentral Gyrus, BA4	3.758	0.001331
6	7	28	97	Cingulate Gyrus, BA24	3.591	0.001946
-32	44	24	168	Middle frontal gyrus, BA10	3.320	0.003602
9	-93	4	1208	Cuneus, BA17	4.458	0.000270
40	38	16	131	Middle frontal gyrus, BA46	3.547	0.002155
-13	-94	0	205	Cuneus, BA17	3.742	0.001381

Results

Behavioural Results

A first analysis of the behavioural data showed a paradoxical result in the load 1 condition of the emotion task with a performance in load 1 similar to load 3. A high percentage of false positive responses were detected. A more thorough analysis demonstrated a significantly higher number of errors when the target had to be rejected ($t = -2.08$, $df = 8.96$, $p = .04$) than in the opposite case. In all other load conditions no significant differences appeared. Post trial interviews with subjects indicated some ambiguity in the load 1 condition due to the fact the trials were not introduced as “emotion” or “identity”. We therefor excluded the load

1 condition from further analysis due to this systematic error. In a behavioural study with 46 healthy subjects (unpublished data) where the same paradigm was used, but each trial were preceded with "emotion" or "identity", false positive answer in the emotion load 1 condition dramatically decreased, showing a robust load effect from load 1 to load 3.

FMRI results

Encoding

A main effect of load ($F(1,19) = 15.2$, p(uncorr.) < 0.001, cluster size threshold at least 10 voxels), driven by higher activation for load 3, was detected in the

Table 3: Brain regions exhebiting significant activity of two-way interactions from ANOVA during delay. X, Y and Z represent coordinates in the Talairach space. t- and p- values are derived from region-of-interest analysis.

LOAD			**Whole Brain p<.005**		**Load 3 > Load 2**	
x	**y**	**z**	**voxel**	**Region**	**t-Value**	**P-value**
18	-18	51	57	medial frontal gyrus, BA6	3.822	0.001151
-18	-27	42	154	Cingulate gyrus, BA 31	4.473	0.000261
21	-39	39	99	Precuneus	3.729	0.001423
-12	-13	4	17	Thalamus	3.488	0.002461
28	48	-8	132	Middle frontal gyrus, BA11	3.036	0.006790
TASK			**Whole Brain p<.005**		**Identity > Emotion**	
x	**y**	**z**	**voxel**	**region**	**t-Value**	**p-Value**
-34	42	0	635	Inferior frontal gyrus, BA10	3.642	0.001734
2	0	-5	43	Anterior cingulate gyrus, BA25	3.349	0.003372
-34	-32	-8	70	Parahippocampal gyrus, BA36	3.286	0.003888
6	-30	-17	159	Cerebellum, anterior lobe	3.597	0.001921
16	2	-17	112	Amygdala	3.275	0.003983
INTERACTION task x load			**Whole Brain p<.005**			
x	**y**	**z**	**voxel**	**region**	**contrast**	**t-Value**	**p-Value**
22	-11	65	498	Precentral gyrus, BA6	ID 2 > ID3	4.176	0.000513
					ID 3 > EMO 3	-2.639	0.016166
39	-27	58	175	Precentral gyrus, BA4	ID 2 > ID 3	2.833	0.010637
					ID 3 > EMO 3	-2.955	0.008129
50	-33	49	511	Postcentral gyrus, BA40	ID 2 > ID 3	2.623	0.016730
					ID 3 > EMO 3	-2.419	0.025751
21	-47	43	510	Precuneus	ID 2> EMO 2	-3.700	0.001520
					EMO 2 > EMO 3	4.927	0.000094

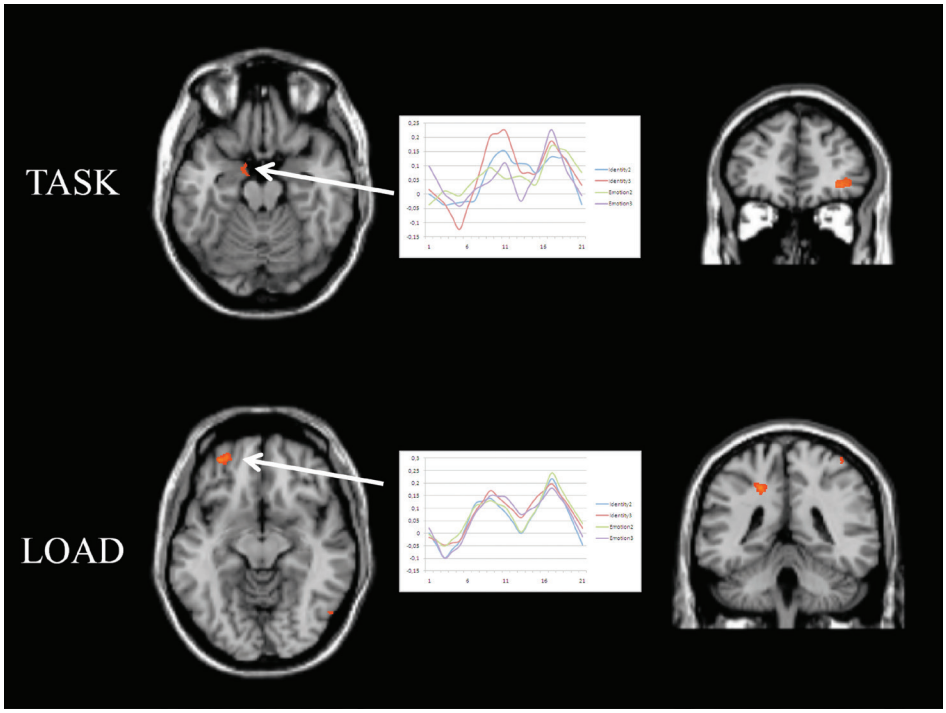

Fig. 3. Axial and coronal slide of the task and load contrast for delay. In the middle column time courses of BOLD signal for the designated clusters (time resolution in seconds). For details of clusters with increased BOLD-signal see text and Table 3.

medial frontal gyrus, cuneus, inferior occipital gyrus and the lingual gyrus of the left hemisphere and in the superior parietal lobe, precuneus, middle frontal gyrus, inferior occipital gyrus and fusiform gyrus of the right hemisphere (Table 1 and Fig. 2). A main effect of task ($F(1,19) = 10.7$, p(uncorr.) < 0.005, cluster size threshold at least 10 contiguous voxels), driven by higher activation for the identity task, was found in the left middle frontal gyrus, precuneus, cuneus, inferior parietal lobule and precentral gyrus and in the right middle frontal gyrus, superior parietal lobule, precuneus and cingulate gyrus (Table 2 and Fig. 2). No area showed a significant interaction between task and load.

Delay

A main effect of load ($F(1,19) = 10.7$, p(uncorr.) < 0.005, cluster size threshold at least 10 contiguous voxels), driven by higher activation for load 3, was detected in the left cingulate gyrus, the left thalamus and the right precuneus and medial and middle frontal gyri (Table 3 and Fig. 3). A main effect of task ($F(1,19) = 10.7$, p(uncorr.) < 0.005, cluster size threshold at least 10 contiguous voxels), driven by higher activation for the identity task, was found in the left inferior frontal and the parahippocampal gyri and the right anterior cingulate gyrus, amygdala and cerebellum (Table 3 and Fig. 3). An interaction between load and task ($F(1,19)$

= 10.7, p(uncorr.) < 0.005) was found in the right pre- and postcentral gyri, and precuneus (Table 3).

Retrieval

A main effect of load (F(1,19) = 10.7, p(uncorr.) < 0.005, cluster size threshold at least 10 contiguous voxels) driven by higher activation for load 3, was detected in the left middle frontal, middle temporal and right superior frontal gyrus (Table 2 and Fig. 4).

Table 4: Brain regions exhebiting significant activity of two-way interactions from ANOVA during retrieval. X, Y and Z represent coordinates in the Talairach space. t- and p- values are derived from region-of-interest analysis

LOAD			**Whole Brain p<.005**			**Load 3 > Load 2**	
x	y	z	voxel	Region		t-Value	p-Value
-20	58	19	554	Middle frontal gyrus, BA10		3.604	0.001891
21	54	3	498	Superior frontal gyrus		2.358	0.029265
-64	-33	-13	16	Middle temporal gyrus, BA21		3.549	0.002145
TASK			**Whole Brain p<.005**			**Identity > Emotion**	
x	y	z	voxel	Region		t-Value	p-Value
64	-46	21	52	Superior temporal gyrus, BA22		-2.709	0.013922
-34	-45	-1	281	Parahippocampal gyrus, BA19		-3.652	0.001696
44	-15	1	48	Middle frontal gyrus, BA6		-3.298	0.003783
59	-31	-17	59	Inferior temporal gyrus, BA6		-3.334	0.003490
49	-12	-24	413	Fusiform gyrus, BA20		-4.810	0.000122
INTERACTION task x load			**Whole Brain p<.005**				
x	y	z	voxel	Region		t-Value	p-Value
-40	-48	55	46	Inf. parietal lobe, BA40	ID 2 > ID 3	-2.790	0.011676
					ID 2> EMO 2	-2.499	0.024204
27	-45	41	97	Precuneus, BA7	ID 3 > EMO 3	-3.079	0,006177
					ID 2 > ID 3	3.979	0.000803
-3	61	18	386	Med. frontal gyrus, BA10	ID 2 > EMO 2	-2.566	0.018888
					ID 3 > EMO 3	2.349	0.029775
					ID 2 > ID 3	-2.400	0.026818
23	-27	12	515	Thalamus	ID 2 > ID 3	-3.282	0.003919
					ID 2> EMO 2	-3.028	0.006912
27	-14	-12	134	Parahipoca. gyrus	ID 2 > ID 3	4.066	0.000660
					ID 2> EMO 2	-3.547	0.002640
-5	-14	-17	333	Pons	ID 2 > ID 3	-2.839	0.010495
					ID 2> EMO 2		

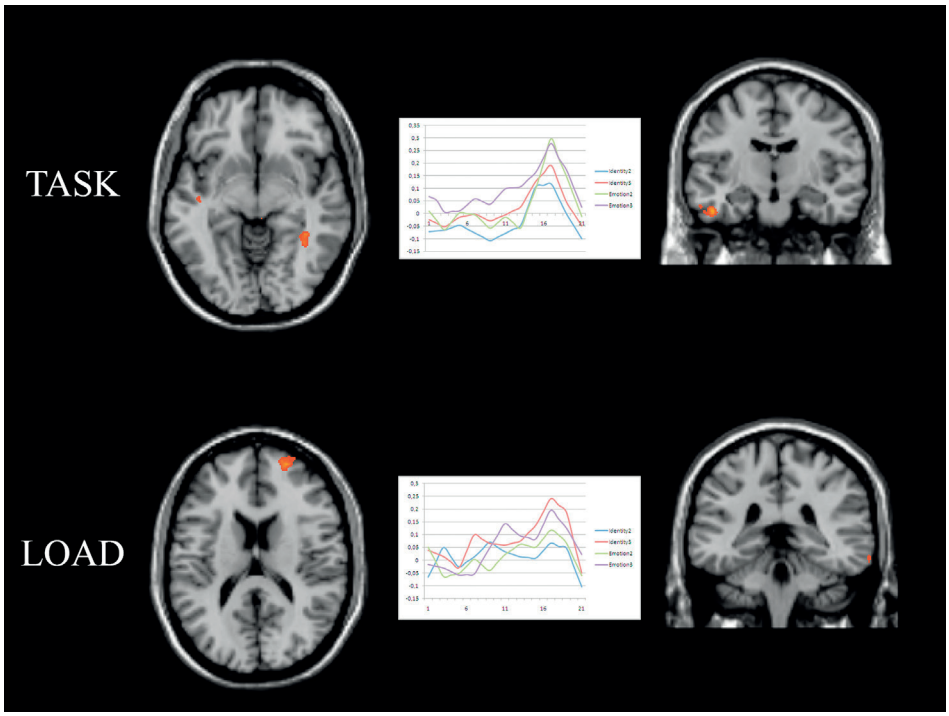

Fig 4. Axial and coronal slide of the task and load contrast for retrieval. In the middle column time courses of BOLD signal for the designated clusters (time resolution in seconds). For details of clusters with increased BOLD-signal see text and Table 4.

A main effect of task ($F(1,19) = 10.7$, p(uncorr.) < 0.005, cluster size threshold at least 10 contiguous voxels) driven by higher activation for the emotion task, was detected in the right inferior and superior temporal, the middle frontal and the fusiform gyrus and the left parahippocampal gyrus (Table 2 and Fig. 4).
An interaction between task and load ($F(1,19) = 10.7$, $df = 19$, p(uncorr.) < 0.005, cluster size threshold at least 10 contiguous voxels) revealed effects in the left medial frontal gyrus, inferior parietal lobe and pons, and the right precuneus, thalamus and parahippocampal gyrus (Table 2). Posthoc t-test revealed that this interaction was mainly driven by lower BOLD signal in condition identity load 2 compared with the other conditions (all p's < 0.05).

Specificity of effects for the delay period

Based on the present design, we cannot completely rule out that task effects during the delay were carried over from the encoding phase. We addressed this issue by adding phase (encoding, delay and retrieval) as a factor to a whole brain 2 (task: identity vs. emotion) × 3 (phase) repeated measurement ANOVA (cluster size threshold at least 10 contiguous voxels). A significant task × phase interaction was observed in the right amygdala: $F(2,38) = 8.3$, $p < 0.001$, the right parahippocampal gyrus: $F(2,38) = 10$, $p = 0.001$, and the left lingual gyrus: $F(2,38) =$

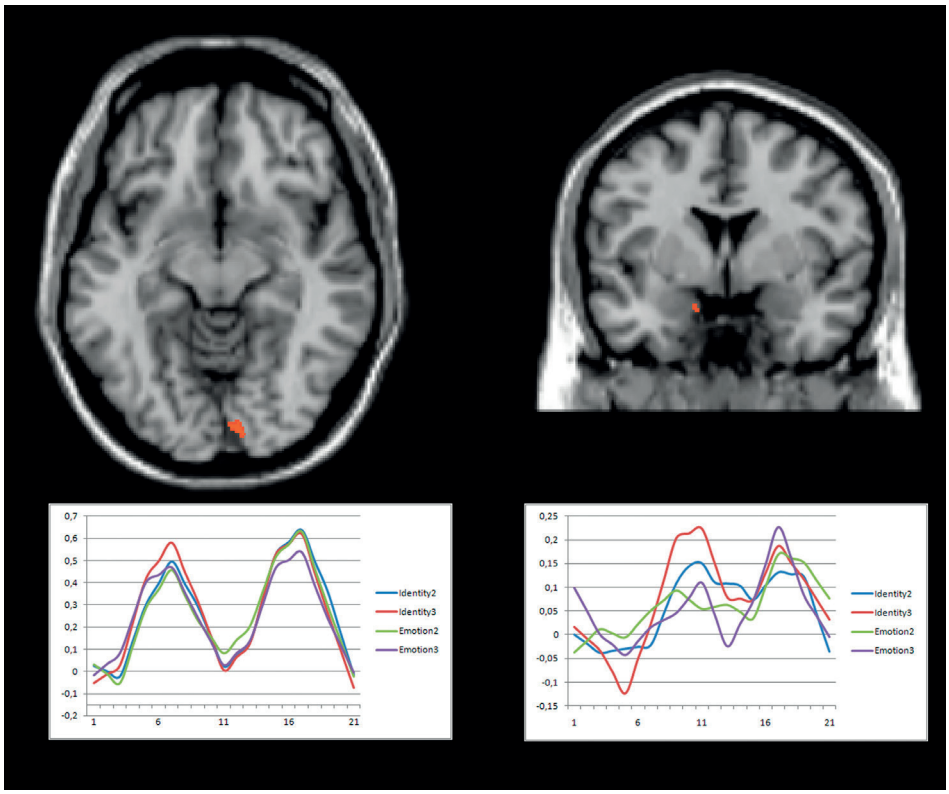

Fig. 5. Axial and coronal slide of the whole brain task by phase interaction. In the upper row two of the three clusters with significant BOLD increase, in the lower row time courses of BOLD signal for the designated clusters (time resolution in seconds). For details of clusters with increased BOLD-signal see text and Table 5.

10, $p < 0.001$ (Table 4 and Fig. 5).

The significant phase by task interaction in the right amygdala supported our finding that differences between emotion and identity in this area were only present in the delay period (posthoc t-test encoding n.s.; delay $t(19) = 3.4$ $p = 0.002$; retrieval n.s.). In the three- way interaction task × phase × load $F(2,38) = 8.3$, $p < 0.001$ only one significant cluster in the right precuneus was observed. Posthoc t- test revealed a significant difference for load in the delay phase: $t(19) = 3.221$, $p < 0.005$. All other posthoc t-test for load and task were not significant.

Covariance analysis with behavioural data

For the cluster of the right amygdala with a significant main effect of the factor task during the delay we calculated an ANCOVA with the mean difference in A' values for the two tasks. We found a significant task effect ($F = 7.5$, $p = 0.01$), indicating that difference between identity and emotion was not driven by any performance differences.

Discussion

Subjects performed better on load 2 than on load 3, but no differences for task and no significant interaction were observed. The main novelty of the present study lies in the differences in brain activation between the maintenance of identity and emotional expression of faces. These task effects were driven by higher activity in the identity condition during encoding in the frontal and parietal lobe and extrastriate visual cortex and during delay in the frontal and medial temporal lobe including the right amygdala and anterior cingulate gyrus. Conversely, activity associated with the emotional expression condition was higher during retrieval in right frontal and temporal areas and fusiform gyrus, and left parahippocampal gyrus.

Load effects

The behavioural load effect conforms to many studies showing decreasing performance with higher number of faces to be maintained in WM [29]. The fMRI load effects correspond to the typical network of visual working memory encoding with BOLD signal enhancement in the frontal, parietal and occipital lobe [29, 36]. In contrast to Druzgal & D'Esposito [36] and Jackson et al. [29] we only find unilateral activation of the fusiform gyrus with increasing load. This may be an effect of comparing only two load conditions. Load effects were additionally seen in the superior parietal lobe, possibly reflecting higher attentional demand with increasing load [37], and in the medial and middle frontal gyrus and occipital lobe [38]. Several of the prefrontal and occipital regions had shown an increased BOLD- signal during encoding of faces in previous studies as well [39-41].

The frontal working memory network was also active during the maintenance phase, again conforming to previous work [42]. In contrast to earlier facial WM studies [36, 43], we did not find load-dependent activation increases in bilateral fusiform gyrus during the delay. This is in keeping with several studies that did not report significant activation in higher visual areas during delay phases of visual WM tasks [1, 37]. No regions of the limbic system, except the left posterior cingulated gyrus showed increased bold signal due to increasing load, probably due to the fact that a variety of different emotions were presented which included faces with neutral expression, similar to Jackson et al. [29].

Emotion vs. identity

This was the first study directly to examine the contrast between WM for identity and emotion. LoPresti et al. [28] compared conditions separately with a control condition, and Jackson et al. [29] only used an identity condition. The higher encoding-related activity in the frontal and parietal lobes in the identity condition may have been an effect of higher attentional demand. We observed a reverse pattern during retrieval, where activity in several areas was higher for the emotion condition. Because these areas included higher visual areas, this may reflect the higher demand on fine-grained visual analysis at the matching stage of the

emotion condition. During delay, higher signal was only observed for the identity condition, for example in the right amygdala and the left parahippocampal gyrus. These two regions showed an increased BOLD-response during active maintenance when comparing faces with a control stimulus, but did not show a task effect in the study by LoPresti et al. [28], which may have been a result of the low load (one face only) used in that study.

The identity task generally resulted in higher BOLD signal than the emotion task during encoding and delay. Interestingly, structures of the limbic system were less active in the emotion condition during the delay period only. The higher amygdala activity in the identity condition may be driven by repetition effects. Gläscher et al. (2004) found that repetitive presentation of faces with the same emotion induced a stronger increase in BOLD signal in the amygdala compared to varying emotions. It thus seems that the amygdala is more responsive to the repeated presentation of the same emotion than to rapidly changing emotional expressions [44]. The role of the amygdala might be to build up automatically a stable representation of the currently relevant and repeatedly presented emotion and to aid its encoding into long-term memory [45], but not so much to track rapid changes of emotional context. This interpretation seems to conflict with the study by Breiter et al. [26], who found a habituation of amygdala activity to the repeated presentation of emotional faces displaying the same emotion. However they compared blocks lasting 36 s which were separated by a time span of 108 s. In the present study a maximum of three faces were presented in a time frame of 2 s, and it thus seems unlikely that habituation due to the repeated stimulation of the same emotion could account for our findings.

In addition to its direct activation by sensory stimuli the amygdala plays an important role in the consolidation of memory [46-48], its attentional modulation [49-51] and arousal effects [52]. The delay-specific task modulation of amygdala activity may thus reflect the more stable emotional representation that was automatically generated in the identity condition and the associated higher arousal.

Additional regions of the paralimbic system in the bilateral parahippocampal gyrus and in the anterior cingulate gyrus, which both receive projections from the amygdala [53], and the cuneus showed an increased BOLD- signal in the identity task as well. These regions have been reported to be more active in response to dynamic compared to static stimuli [54, 55]. The brief presentation of facial stimuli with varying identity may produce the same effect. The cerebellum showed increased BOLD-response in the identity condition during delay as well. Several other studies [28, 43, 56] found activation in the cerebellum during facial working memory tasks, but its functional role has remained unclear. Hautzel, Mottaghy, Specht, Muller, and Krause [57] suggested that the extensive involvement of the cerebellum during WM tasks is owed to its contribution to executive processes. A recent meta-analysis [58] has suggested a different topography of cerebellar BOLD- signal changes for the phases of WM tasks, but further research seems necessary to elucidate the specific role of the cerebellum.

A limitation of our paradigm was that it did not allow for separation of the influence of specific emotions, as investigated by Jackson et al. [29]. The advantage of our procedure is that we were able to examine the difference between identity and emotion in a WM paradigm.

A further limitation is that our approach does not completely rule out carry-over effects from the encoding into the delay phase. In working memory studies the BOLD signal change for a given trial phase (encoding, delay retrieval) is not independent of the BOLD response from earlier trial phases (colinearity problem and carry over effects, e.g., Dale & Buckner, [59]). This reduces the accuracy in estimating the portions of the BOLD response attributable to each phase separately [60-62].

Different designs have been used to address this problem in working memory studies. One method has been to jitter the duration of the maintenance interval [60], but this does not eliminate the colinearity problem [63] and the variable duration of the delay phase induces several new cognitive processes and task demands which need to be controlled as separate factors. Another option is the use of delay intervals of more than 20 s [64], resulting in long measurement times and potentially consolidation processes that go beyond classical working memory. A third possible way to control this problem is to model only the middle or later parts of the maintenance response [34, 65, 66]. All these described methods (jitter; long delay phases; model late parts of the delay) reduce the influence of the encoding-related BOLD responses on maintenance-related effects, but do not entirely eliminate the colinearity problem [63]. We therefore decided on modelling the late parts of the delay only (similar to Postle, [34]; with a time gap of 4 s between off-set of the encoding and on-set of the delay predictor) because this design is an efficient without extremely long delay phases.

Further research is needed to assess whether there is a specific WM system for emotionally salient stimuli, and whether it is further subdivided according to categorical emotions. A further limitation is that in order to obtain perfect estimates of brain activity for separate task phases we would have had to jitter the duration of the delay. In the present study we did not use this method, because jittering would also introduce a new factor into the cognitive task, which would have to be modelled in the GLM (with sufficient number of trials per jitter), resulting in very long measurement-times.

In conclusion we describe a network of frontoparietal, limbic and cerebellar brain regions that were more active during the maintenance of identity compared to the emotional expression of faces. These areas, which included the right amygdala, responded more strongly to stable than changing emotional facial expression. Repeated presentation of faces with similar expressions may be needed to build up stable representations of emotions in the amygdala, which will then aid memory for emotional stimuli [67]. Ours is the first study to demonstrate such an effect for memory over brief time scales.

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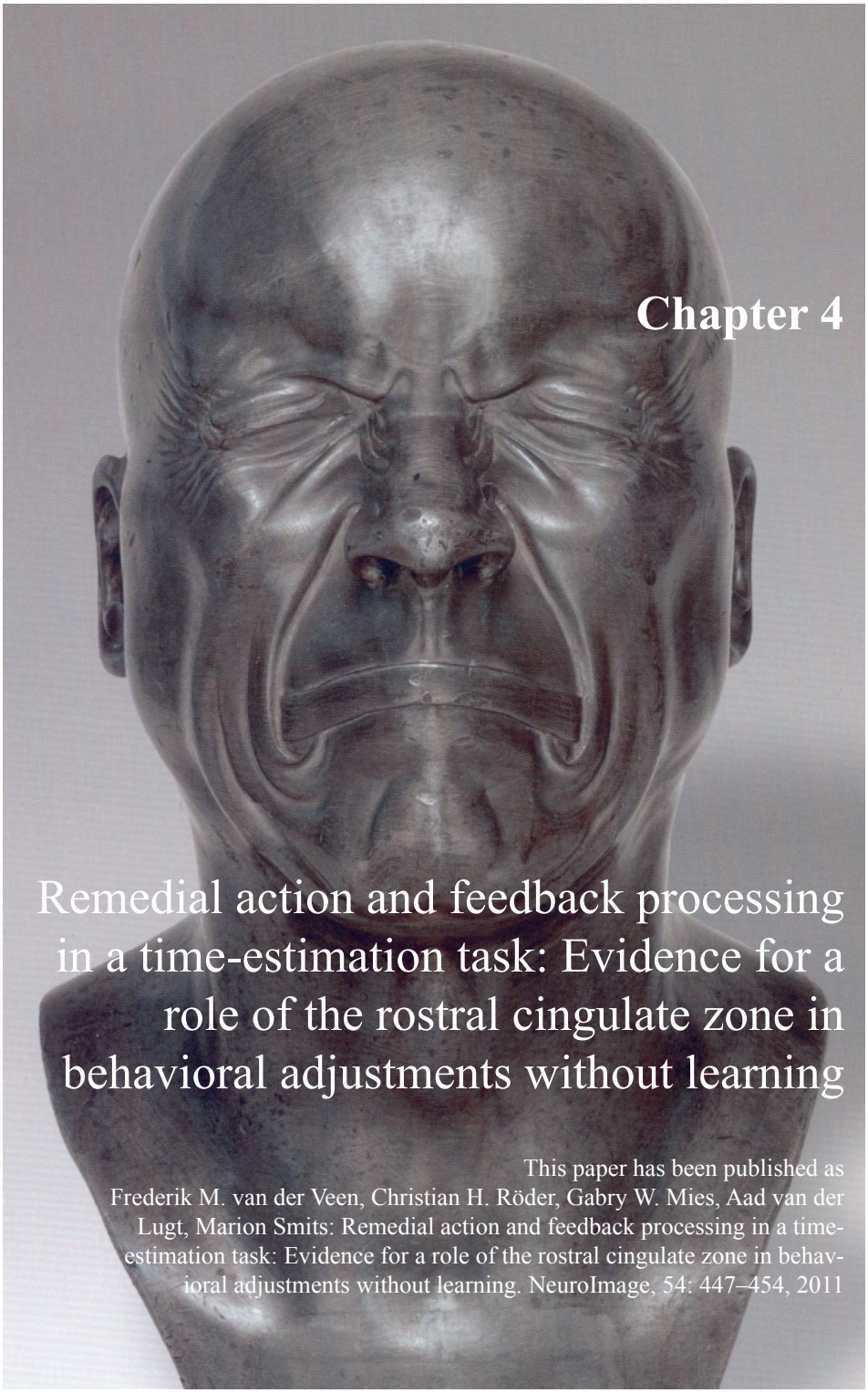

Chapter 4

Remedial action and feedback processing in a time-estimation task: Evidence for a role of the rostral cingulate zone in behavioral adjustments without learning

This paper has been published as
Frederik M. van der Veen, Christian H. Röder, Gabry W. Mies, Aad van der Lugt, Marion Smits: Remedial action and feedback processing in a time-estimation task: Evidence for a role of the rostral cingulate zone in behavioral adjustments without learning. NeuroImage, 54: 447–454, 2011

Abstract

The present study examined the role of the rostral cingulate zone (RCZ) in feedback processing, and especially focused on effects of modality of the feedback stimulus and remedial action. Participants performed a time-estimation task in which they had to estimate a 1-second interval. After the estimation participants received verbal (correct/false) or facial (fearful face/happy face) feedback. Percentage of positive and negative feedback was kept at 50% by dynamically adjusting the interval in which estimations were labeled correct. Contrary to predictions of the reinforcement learning theory, which predicts more RCZ activation when the outcome of behavior is worse than expected, we found that the RCZ was more active after positive feedback than after negative feedback, independent of the modality of the feedback stimulus.

More in line with the suggested role of the RCZ in reinforcement learning was the finding that the RCZ was more active after negative feedback that was followed by a correct adjustment as compared to negative feedback followed by an incorrect adjustment. Both findings can be explained in terms of the RCZ being involved in facilitating remedial action as opposed to the suggested signaling function (outcome is worse than expected) proposed by the reinforcement learning theory.

Introduction

In a constantly changing environment it is important to monitor whether current behavior is appropriate. This can be done by either internally assessing successfulness of ongoing behavior or by using externally generated feedback stimuli. In the last two decades performance monitoring has received a lot of attention, especially after the discovery of the Error Related Negativity (ERN), an event related brain potential (ERP) component that is elicited by errors [1, 2]. More recently, a negative component accompanying negative feedback stimuli was discovered and due to a similar scalp distribution and underlying sources it was suggested that this component was equivalent to the ERN and was called Feedback ERN, or FRN [3]. Source localization studies of both the ERN and the FRN have localized the sources in the Anterior Cingulate Cortex [3, 4] and numerous imaging studies have confirmed this location (e.g. [5, 6]. Both the FRN and the ERN have been related to a reinforcement learning signal that is generated in the mesencephalic dopamine system when outcome of behavior is worse than expected [7]. This error signal is sent to the ACC where it can be used to adapt behavior.

Although various studies have reported slightly different brain areas as the generator of the ERN [8], the literature has been quite consistent with generators in or close to the dorsal part of the ACC. Negative feedback, on the other hand, is inconsistently accompanied by activation in the dorsal part of the ACC.

Although numerous studies found activation in the ACC during the presentation of negative feedback (e.g. [6, 9, 10], others have failed to do so (e.g. [11]. Moreover, Nieuwenhuis et al. [12] and van Veen et al. [13] could not find any additional brain activation to negative feedback as compared to positive feedback in a time-estimation paradigm. Especially these last two findings are intriguing, given the fact that in ERP studies negative feedback consistently evokes an FRN using the same paradigm [3, 12, 14, 15]. Nieuwenhuis et al. who examined both the FRN and BOLD responses in two separate experiments argued that the lack of activity in the dorsal ACC in the time-estimation task might be due to the equal probability of positive and negative feedback. However, this cannot explain the lack of ACC activation in the study of Cools et al. [11] who did not find additional dorsal ACC activation to negative feedback with a low probability. It should be noted, however, that Cools et al. did find additional activation in the dorsomedial prefrontal cortex relatively close to the ACC. Nieuwenhuis et al. did find a strong FRN in the same time-estimation task, but they found that the underlying sources of the FRN were not localized in the dorsal ACC, but in the posterior cingulate cortex and the rostral part of the ACC.

The lack of additional activation to negative feedback in the studies of van Veen et al. [13] and Nieuwenhuis et al. [12] could be due to a number of factors such as the relatively small number of participants in both studies and the use of neutral feedback stimuli. In the current study we examined the feedback-related brain activation in a time estimation paradigm and examined the effect of different types of emotional stimuli by comparing verbal feedback with facial expressions

as feedback stimuli. It was expected that using facial expressions, which have a more direct emotional value would enhance the feedback-related brain activation compared to verbal stimuli, which have a more indirect emotional value, and would lead to stronger activation in the areas associated with feedback processing.
Furthermore, the studies of van Veen et al. [13] and Nieuwenhuis et al. [12] did not examine the effect of behavioral adjustments on the brain response to the feedback stimulus. A recent study of Holroyd and Krigolson [16] showed that the FRN in a time-estimation paradigm was sensitive to adjustment behavior following the feedback stimulus. They showed that the absolute change in response time was positively correlated with the amplitude of the FRN. However, absolute change is a relatively crude measure of adjustment behavior and adjustment behavior was only compared between participants and conditions and not examined for individual trials. Therefore, in the present study we aimed at using a measure that is more strongly related to the quality of the adjustments and examined activation differences within subjects. For this purpose we compared negative feedback followed by correct and incorrect adjustments. Correct was defined as a change towards the instructed goal of 1 s, i.e., shortening the next estimation when the current estimation was too long or lengthening the next estimation when the current estimation was too short. Previous studies, which examined cardiac responses to feedback stimuli [15, 17, 18], have found that negative feedback followed by correct adjustments is associated with a stronger response. Furthermore, a relation between BOLD responses in areas falling within or overlapping with the RCZ has been related to other forms of remedial action such as post-error slowing [19-21], and therefore we hypothesize that feedback followed by correct adjustments would be accompanied by stronger BOLD responses in the areas associated with feedback processing.

Methods

Participants

Twenty healthy volunteers (14 male, 6 female; mean age=20) participated in this study. All participants were screened for neurological, psychiatric and other illnesses interfering with the measurement of normal brain function with an extensive questionnaire and screened for MRI contra-indications. The study was approved by the medical ethics committee of the Erasmus Medical Center Rotterdam. All volunteers gave written informed consent and were paid 25 Euros for their voluntary participation.

Task

The task was based on the time-estimation task developed by Miltner et al. [3] (1997). Participants were asked to estimate a 1-second interval each time an exclamation mark (‘!’) was presented on a screen. The estimated 1-second interval started with the onset of the exclamation mark and ended with the button press.

After the button press a star ('*') was presented in the center of the screen for 1 s followed by a feedback signal which was presented for 1 s and finally another star '*' was presented for 2 s. After the presentation of this last star the next trial started. Feedback was based on the estimation of the participants. A response was labeled as correct when the response fell within an a priori determined time interval. At the start of the task this interval was between 900 ms and 1100 ms after the onset of the exclamation mark. The interval was dynamically adjusted to derive about equal proportions of positive and negative feedback. After a correct response the interval was shortened with 20 ms and after an incorrect response the interval was lengthened with 20 ms.

Two types of feedback were presented, that is, words and facial expressions. For the first type of feedback the Dutch word 'GOED', which means correct, was presented for correct estimations and 'FOUT', which means incorrect, for incorrect estimations. For the second type of feedback, a face from the Ekman and Friesen [22] series of emotional faces was presented. A happy expression was presented after a correct response and a fearful expression was presented after an incorrect response. Four different faces were selected (two male, two female) and both the happy and fearful expressions of these faces were used as feedback stimulus.

Procedure

The task was explained without mentioning the dynamic interval and practiced before the scanning session and the task was practiced a second time in the scanner directly preceding the actual scanning started. Participants performed the task twice in two scanning sessions consisting of 88 stimuli each with a short break between the two sessions during which the subject stayed in the scanner. In each block participants received 50% verbal and 50% facial feedback, and type of feedback was varied in a pseudo-random way. The time-estimation task was part of an experiment in which the participants also performed three sessions of a working memory task. The order of the time estimation task and working memory task was balanced between participants and the two tasks were separated by a structural scan which lasted about 5 min. Total time spent in the scanner was about 1 h.

MRI acquisition and preprocessing

Scanning was performed on a 3 T GE scanner (General Electric, Milwaukee, USA). For the functional scans a single-shot gradient-echo echo-planar imaging (EPI) sequence was used, which is known to be sensitive to the blood oxygen level dependent (BOLD) contrast. Important scan parameters were repetition time (TR) = 2000 ms, echo time (TE) = 30ms, number of slices=26, slice thickness=3.5 mm, slice gap=.5 mm and in plane resolution of 1.7 x 1.7 mm. Two functional scanning sessions were performed, in which 230 volumes were acquired, preceded by 5 dummy full brain scans which were not used in the analysis. For anatomical reference, a 3D high resolution inversion recovery fast spoiled gradient

recalled echo T1 weighted
sequence was used, which covered the whole brain. Important parameters for this session were number of slices=192, effective slice thickness = .80 mm, and in plane resolution 0.49 x 0.49mm. Data analysis was performed using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Preprocessing steps consisted of reorienting, slice time correction, realignment using the first slice as a reference and unwarping. Furthermore, the functional images were co-registered to the structural image and both the functional and structural images were normalized using the Montreal Neurological Institute T1 template. The functional images were spatially smoothed using a Gaussian kernel of 8 mm full width at half maximum and temporally smoothed with a high pass filter of 128 s.

Statistical analysis

Performance was analyzed using SPSS 16 for Windows. First, we analyzed flexibility of behavior, which was defined as the percentage of correct adjustments after a negative feedback signal. A correct adjustment was defined as an adjustment towards the goal of 1 s, in other words a shorter estimation following a too long estimation or a longer estimation following a too short estimation. Second, we examined the accuracy of the estimations, which was defined as the mean length of the interval in which a response is labeled as correct. Finally, we examined average estimation time, percentage of negative feedback and absolute size of the change in estimation time after a feedback signal to be certain that all aspects of behavior in this task were fully examined.

For the imaging data an event-related approach was used. In a first analysis four different types of feedback events were modeled. We separately modeled positive and negative facial feedback and positive and negative verbal feedback. Three t-contrasts were computed: 1. Positive−Negative Feedback (main effect Valence) 2. Facial−Verbal Feedback (main effect Modality) 3. (Positive − Negative Facial Feedback) − (Positive − Negative Verbal Feedback) (Interaction: Valence x Modality). For these analyses on average 89±1 (± standard error of the mean; SEM) negative, 87±1 positive, 88 (fixed) facial and 88 (fixed) verbal feedback trials were included.

In a second analysis we modeled six separate events, that is, positive facial and verbal feedback, negative verbal and facial feedback followed by a correct performance adjustment and negative verbal and facial feedback followed by an incorrect performance adjustment. In this analysis one t-contrast was computed: Negative feedback followed by a correct performance adjustment vs. negative feedback followed by an incorrect performance adjustment. For these analyses on average 66±1 negative feedback trials followed by a correct adjustment and 22±1 negative feedback trials followed by an incorrect adjustment were included. For both analyses the individual contrast images were used in a second-level analysis in which these images were further tested using a one-sample t-test. First, a

whole-brain analysis was performed in which a height threshold of $p < .001$ and an extent threshold of 10 voxels were used. Significant voxels and clusters are reported as significant if $p < .05$ corrected using the family wise error approach. The Talairach Daemon database [23] was used to label the significant clusters. Second, a region of interest (ROI) analysiswas performed using Marsbar [24]. We selected five ROIs based on their presumed role in feedback processing (Rostral cingulate zone, RCZ, defined as 8 mm sphere around Talairach coordinates ±8, 30, 32 and pre-SMA defined as a 8 mm sphere around Talairach coordinates ±8, 8, 60, both based on Mars et al. [25]; Nucleus accumbens defined as an 8 mm sphere around ±10, 12, −2, based on Knutson et al. [26]), in emotion (Amygdala; derived from the AAL map, Tzourio-Mazoyer et al., [27]) and face processing (Fusiform gyrus; derived from the AAL map, Tzourio-Mazoyer et al., [27]). For all ROIs we computed the average beta value separately for 4 predictors (positive facial, positive verbal, negative facial and negative verbal feedback) and separately for the right and left hemispheres and exported these beta values to SPSS. In SPSS we performed a repeated-measures general linear model (GLM) analysis with hemisphere, modality and valence as within-subjects factors. For all ROIs we performed a second analysis with the average beta values of the 6 predictors of the second model (positive facial, positive verbal, negative facial followed by correct or incorrect adjustment, negative verbal followed by correct or incorrect adjustment) and performed a GLM analysis with hemisphere, modality and correctness of adjustment (negative feedback followed by correct adjustment vs. negative feedback followed by incorrect adjustment) as within-subjects factors. Finally, for all ROIs we performed two additional GLM analyses with the behavioral measures as covariates (between subjects factor, one single value per subject). In two separate analyses we included as covariates the average length of the interval in which the estimation was labeled as correct (accuracy) and the percentage of correct adjustments after negative feedback (flexibility). Both measures were tested separately because these measures correlated significantly. Performance measures were centered using the method of Delaney and Maxwell [28], because of a large sum-of-squared error resulting from the addition of these measures as a covariate in the analyses. We used the mean minus the mean of all participants [28, 29].

Results

Performance

On average the participants received 50.9%±.6% (standard error of the mean; SEM) negative feedback, and this percentage did not differ between the two runs, between facial and verbal feedback and was not statistically different from the percentage of positive feedback. This shows that our task manipulation succeeded in controlling the proportion of positive and negative feedback. The percentage of correct adjustments after receiving negative feedback was not affected by stimulus mode, $F(1,19)<1$. Participants corrected their estimation after 75%±1.4%

of the negative feedback stimuli. The average length of the interval in which estimations were labeled as correct was 234±11ms and the average estimation time was 1047±170 ms. As expected, the absolute change in estimation time after a positive feedback stimulus (116 ms±68ms) was smaller than after a negative feedback stimulus (191 ms±129 ms), $F(1,19) = 52.8$, $p < .000001$, but did not differ between verbal and facial feedback, $F(1,19)<1$. Percentage of correct adjustments, length of interval, absolute change in estimation time and estimation time itself did not differ between the two runs, all $Fs<1$, which shows that participants did not improve performance over time.

Brain activation

Whole-brain analysis

Valence: Positive feedback stimuli were accompanied by stronger activation in the right precentral gyrus, bilateral putamen and the lingual gyrus as compared to negative feedback (see Fig. 1 and Table 1). In the opposite comparison, no significant effects could be found.

Stimulus mode: Facial feedback stimuli as compared with verbal feedback stimuli were accompanied by stronger activation in a large cluster including a number of occipital areas with strongest focus in the lingual gyrus and some activation in the fusiform gyrus (see Fig. 2 and Table 2). A second cluster was found in the left inferior temporal gyrus. Verbal feedback, on the other hand, was not associated with stronger brain activation as compared to facial feedback.

Valence*Stimulus mode: Neither the contrast ((positive words − negative words) − (positive faces − negative faces)) nor the contrast ((positive faces − negative faces) − (positive words − negative words)) yielded a significant result.

Behavioral adjustment: In the contrast between negative feedback stimuli that

Table 1. Significant brain activation in the contrast positive minus negative feedback

Region of activation	Hemsp.	BA	Cluster size	Z-score	MNI-coordinates
Pos > Neg	L				
Claustrum	R		213888	5.17	-32 8 -10
Putamen	R		a	4.83	30 -4 2
Precentral gyrus	R	4	a	4.59	32 -22 46
Putamen	R		a	4.68	24 6 0
Subcallosal gyrus	R	34	a	4.62	28 6 -12
Subcallosal gyrus	L	34	a	4.61	26 8 -16
Putamen	R		a	4.60	-32 -12 2
Cunes	L	17	1189	4.74	20 -96 -4
Medial frontal gyrus	L	6	368	4.70	-14 -26 58
Inferior frontal gyrus	L	46	339	4.15	-46 40 2

a Signficant local maximum in the main cluster described on the first line

were followed by either correct (COR) or incorrect adjustments (INCOR) we found stronger activation in the left superior parietal cortex and left dorsolateral prefrontal cortex for COR as compared to INCOR (see Fig. 3 and Table 3).

ROI analysis

Main model: Activation in terms of beta values for all ROIs was tested in a model with hemisphere, stimulus mode and valence as within subjects factors. For the RCZ we found a two-way interaction between valence and hemisphere, $F(1,19) = 10.0$, $p < .01$. Follow-up analyses showed that only the left RCZ was more strongly activated for positive feedback in comparison to negative feedback, $p < .01$ (see Fig. 1). For the pre-SMA we did not find effects. Amygdala activation was significantly affected by valence, $F(1,19) = 20.0$, $p < .0005$, stimulus mode, $F(1,19) = 10.4$, $p < .005$, and hemisphere, $F(1,19) = 4.7$, $p < .05$. In general, positive feedback and facial feedback led to a stronger activation of the amygdala as

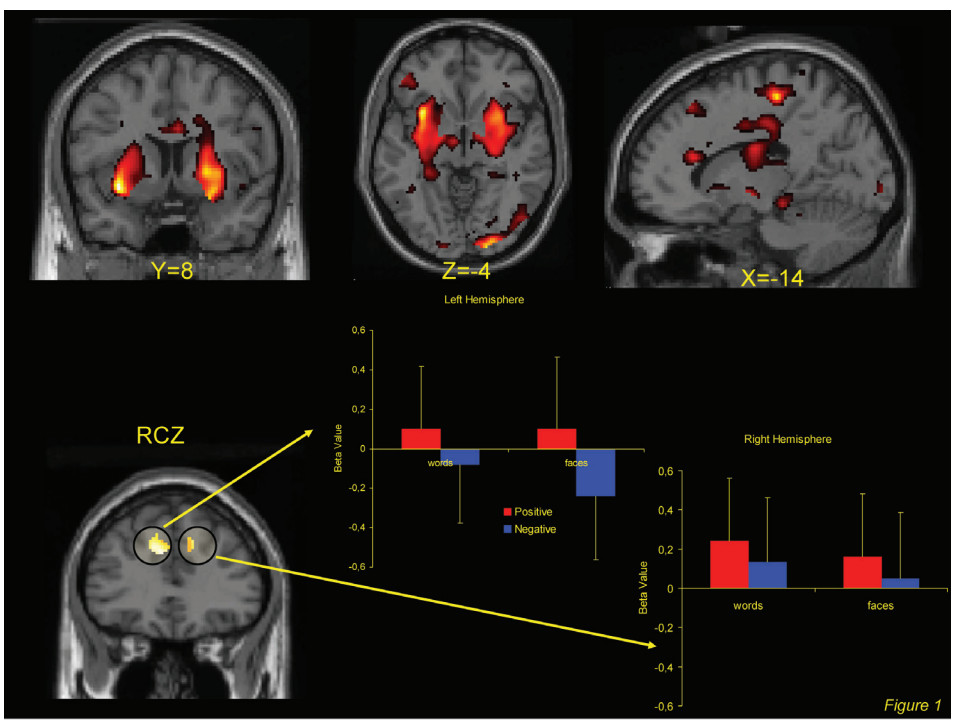

Fig 1. Activation maps and bar graph for the contrast positive minus negative feedback. In the top panel significant (whole-brain analysis, pb.001, clusters of at least 10 voxels) voxels are shown in the coronal (at Talairach coordinate y=8), axial (at Talairach coordinate z=−4) and sagittal plane (at Talairach coordinate x=−14). In the bottom panel significant (ROI analysis, pb.05) voxels are shown in the pre-defined rostral cingulate zone in the coronal plane (at Talairach coordinate y=34), combined with bar graphs showing the beta values (±standard error of the mean) for the four predictors, separately for the left and right hemispheres.

Table 2 Significant brain activation in the contrast facial minus verbal feedback

Region of activation	Hemsp.	BA	Cluster size	Z-score	MNI-coordinates
Faces > Words					
Lingual gyrus	L	19	11162	6.45	-10 -66 -6
Lingual gyrus	L		a	6.21	-10 -80 -4
Lingual gyrus	L/R	18	a	6.13	6 -80 -4
Lingual gyrus	R	19	a	5.78	8 -84 -2
Culmen	R		a	5.78	10 -64 -6
Declive	L		a	5.53	-20 -60 -16
Lingual gyrus	L/R	18	a	5.48	6 -84 -10
Cuneus	R	17	a	5.08	18 -78 8
Cuneus	L/R	18	a	5.02	14 -84 16
Cuneus	R	119	a	4.98	6 -82 32
Declive	R		a	4.82	-36 -66 -14
Lingual gyrus	L	17	a	4.81	-18 -82 4
Parahippocampal gyrus	L	18	a	4.78	-36 -70 -12
Inferior frontal gyrus	R	19	a	4.77	-20 -56 -4

a Signficant local maximum in the main cluster described on the first line

compared to negative and verbal feedback, and brain activation was somewhat stronger in the right as compared to the left hemisphere. For the fusiform gyrus we found significant main effects for stimulus mode, $F(1,19) = 22.2$, $p < .0005$, hemisphere, $F(1,20) = 12.7$, $p < .005$, and valence, $F(1,19) = 7.9$, $p < .05$. As expected, the facial feedback stimuli were followed by a stronger response in the fusiform gyrus, as compared to verbal feedback stimuli. Furthermore, stronger responses were found for positive feedback and in the left hemisphere. An interaction was found between stimulus mode and hemisphere, $F(1,19) = 7.7$, $p < .05$. Follow-up analyses showed that, although for both hemispheres responses were stronger for facial feedback stimuli, the difference between facial and verbal feedback was strongest in the right hemisphere. For the nucleus accumbens we found a main effect of valence, $F(1,19) = 8.1$, $p < .05$, caused by a stronger activation following positive feedback.

Behavioral adjustment: Activation in all ROIs was tested in a model with hemisphere, stimulus mode and type of adjustment (correct vs. incorrect) as within-subjects factors. For the nucleus accumbens we did not find any significant effects. For the pre-SMA we found a main effect of type of adjustment, $F(1,19) = 4.6$, $p < .05$, and for RCZ this effect was near-significant, $F(1,19) = 3.3$, $p=.08$. In both areas this effect was caused by stronger activation after negative feedback followed by correct adjustments. For the amygdala we found main effects of stimulus mode, $F(1,20) = 4.4$, $p < .05$, and hemisphere, $F(1,19) = 5.1$, $p < .05$. For

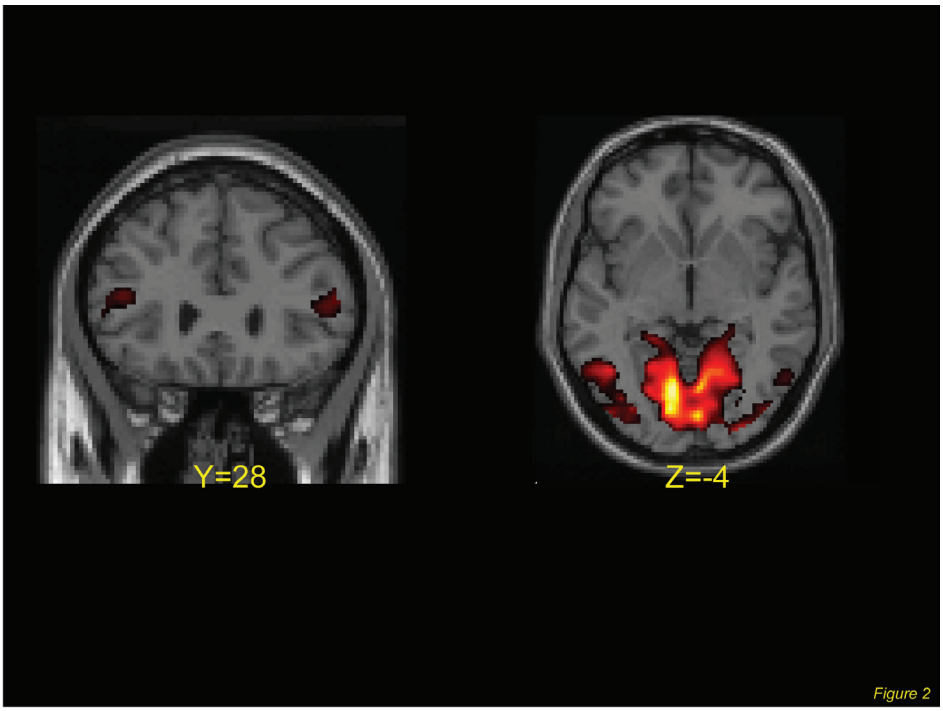

Fig. 2. Activation maps for the contrast facial minus verbal feedback. Significant (wholebrain analysis, pb.001, clusters of at least 10 voxels) voxels are shown in the coronal (at Talairach coordinate y=28), and axial (at Talairach coordinate z=−4) plane.

the fusiform gyrus we also found a main effect of stimulus mode, $F(1,19) = 23.6$, $p < .0005$, and hemisphere, $F(1,19) =$, $p < .05$. Like in the main model, this was caused by stronger activation for facial feedback stimuli.

Covariation: BOLD response and performance: Additional GLM analyses with the behavioral measures as covariates revealed for our model with accuracy as covariate no significant covariation in the RCZ, pre-SMA and nucleus accumbens. However, our accuracy measure covaried with activation in the amygdala, as was shown by a main effect of accuracy, $F(1,18) = 8.3$, $p < .01$, and a three-way interaction between valence, hemisphere and accuracy, $F(1,18) = 5.9$, $p < .05$. Follow-up analyses showed that activation in the amygdala correlated negatively with accuracy (longer intervals go together with more activation), which was significant for all types of feedback and both hemispheres, except for positive facial feedback in the left hemisphere. For the fusiform gyrus we also found a main effect of accuracy, $F(1,18) = 7.8$, $p < .05$ and an interaction between accuracy and valence, $F(1,18) = 4.7$, $p < .05$. Follow-up analyses showed that activation in the fusiform gyrus correlated negatively with accuracy, and these correlations were strongest for negative feedback. Fig. 4 shows the strongest example of the covariation between accuracy and brain activation in the fusiform gyrus, i.e., covariation between beta values of the left fusiform gyrus for negative facial feedback.

For our model with flexibility as covariate, we did not find covariation in the RCZ, fusiform gyrus and nucleus accumbens. However, for the pre-SMA we found a two-way interaction between valence and flexibility, $F(1,18) = 4.4$, $p < .05$, and a three-way interaction between flexibility, hemisphere and modality, $F(1,18) = 8.8$, $p < .01$. Follow-up analyses showed non-significant, mostly negative correlations with flexibility which were somewhat stronger (more negative) in the right hemisphere, and this difference between hemispheres was strongest for verbal feedback. Our flexibility measure also significantly covaried with activation in the amygdala, as was shown by a two-way interaction between modality and flexibility, $F(1,18) = 5.9$, $p < .05$. Follow-up analyses showed nonsignificant negative correlations with flexibility, which were strongest ($p = .09$) for negative verbal feedback in the left hemisphere.

To summarize, the accuracy of performance was negatively correlated with brain activation especially in the amygdala and the fusiform gyrus. The relation between flexibility and brain activation and the relation between accuracy and brain activation in other areas were less clear.

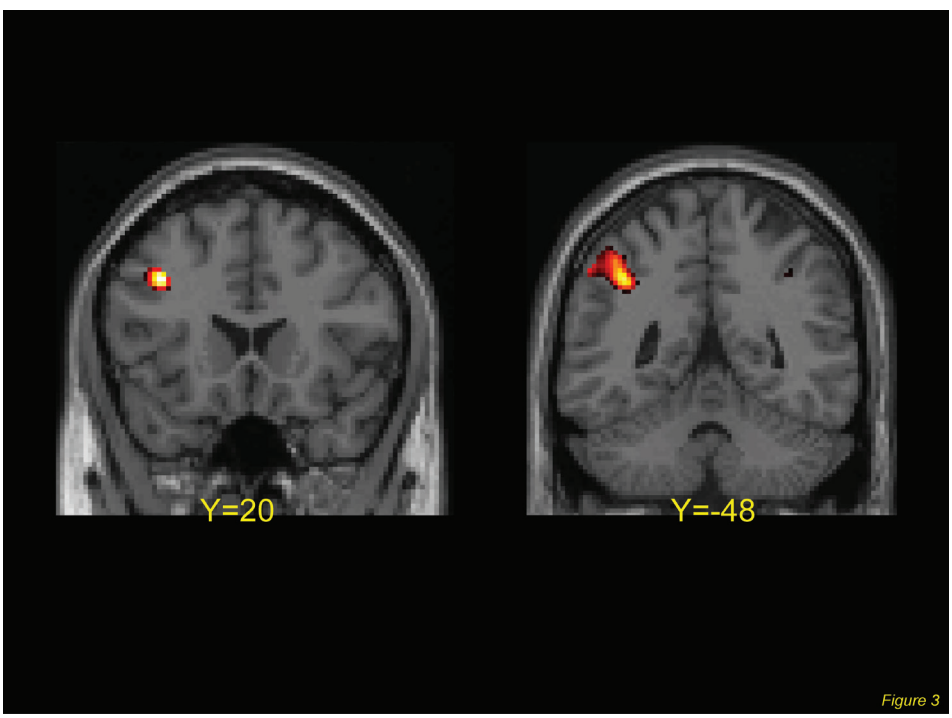

Fig. 3. Activation maps for the contrast negative feedback followed by correct adjustment minus negative feedback followed by incorrect adjustment. Significant (whole-brain analysis, pb.001, clusters of at least 10 voxels) voxels are shown for two slices in the coronal plane (at Talairach coordinate y=20 and y=−48). The frontal slice shows activation in the middle frontal gyrus and the parietal shows activation in the inferior parietal lobule.

Discussion

In the present study the effects of feedback type (emotional faces vs. neutral words) and performance adjustments on feedback-related brain activation were examined. It was found that type of feedback did not interact with the difference between positive and negative feedback. Facial feedback did activate a more extended network of areas in the brain as compared to verbal feedback, but type of feedback did not modulate the difference between positive and negative feedback. For both facial and verbal feedback no additional activation could be found

Table 3 Significant brain activation in the contrast negative feedback followed by correct adjustments (negative correct) minus negative feedback followed by incorrect adjustments (negative incorrect).

Region of activation	Hemsp.	BA	Cluster size	Z-score	MNI-coordinates
Negative correct > negative incorrect					
Middle frontal gyrus	L	9	248	4.17	-38 20 34
Inferior parietal lobule	L	40	411	4.02	-38 -48 40

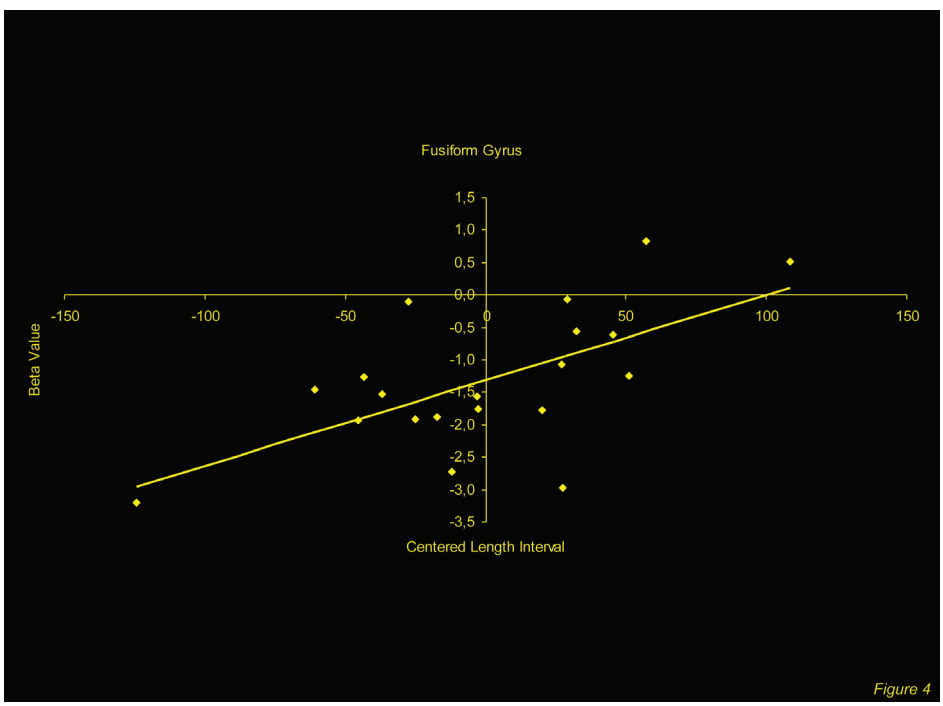

Fig 4. Scatter plot of beta values representing activation in the left fusiform gyrus for the predictor negative facial feedback vs. the length of the interval in which the estimation is labeled correct (this performance measure was centered using the method of Delaney and Maxwell [28]; see Methods for details), which is a measure of estimation accuracy (see Methods for details).

for negative feedback as compared to positive feedback. Positive feedback, on the other hand, activated a more extended network in the brain as compared to negative feedback. Negative feedback stimuli followed by correct performance adjustments activated the RCZ, pre-SMA and parietal and dorsolateral prefrontal areas. Accuracy of performance was negatively correlated with brain activation in the amygdala and the fusiform gyrus.

It was hypothesized that the earlier reported lack of activation in the ACC accompanying negative feedback [12, 13] might be related to the low affective value of the feedback stimuli used in these studies. Therefore, in the present study feedback was presented in the form of meaningful words with a positive or negative meaning and faces with positive or negative expressions. Contrary to the hypothesis, the RCZ showed more activation in the positive as compared to the negative feedback condition. This was not in accordance with the findings of van Veen et al. [13] and Nieuwenhuis et al. [12], who did not report additional activation to positive feedback in this specific region. This apparent discrepancy might be related to differences in analyzing the ROI data and specific definitions of ROIs. We have chosen to use the definition of the RCZ as used by Mars et al. [25], and used Marsbar to extract a single beta value for this area whereas both other studies used different methods and definitions to examine activation in this area. Nieuwenhuis et al. [12] only performed a whole-brain analysis comparing negative feedback and positive feedback and controlled for differences due to poor performance and found no differences, even at a very liberal threshold. Van Veen et al. [13] performed 3 separate ROI analyses based on areas that were active after errors in a Stroop task performed by the same participants. These ROIs differed slightly from our RCZ, but, interestingly, van Veen et al. [13] also found higher beta values for positive feedback as compared to negative feedback for all three areas, but these differences were not significant. A second reason for the discrepancy might be the number of participants included in the studies. In the present study more participants were included, which led to more power in our statistical tests.

The finding of more RCZ activation to positive feedback does not fit the reinforcement learning theory of Holroyd and Coles [7] because positive feedback clearly cannot be worse than expected. Any interpretation in terms of expectation seems to be problematic in this task, because the combination of the difficult task and the dynamic interval used to determine whether an estimation is labeled as correct or not, makes it difficult to build up a proper expectation of the upcoming feedback signal[1].

1 An anonymous reviewer suggested that it might be possible to take the deviationof each response from the time window into account and that this might lead to a rough estimate of expectation–violation. In order to test this we have performed asplit-half analysis on the basis of the distance between the actual estimation and the goal. If expectancy plays a strong role in this task it should be the case that estimations that are relatively closer to the goal would lead to relatively more

An alternative account of the larger activity of the RCZ following positive feedback may be found in the way information provided by the feedback stimulus can be used to adjust performance in the next trial. We would like to speculate that one possibility is that positive feedback in the present task gives clearer cues about how to perform the task than negative feedback. Negative feedback only tells the participant to change behavior, whereas positive feedback gives a clear cue that the next estimation has to be comparable to the previous estimation, which can be seen as more informative, especially in the context of a relatively large percentage of negative feedback. In this way, the stronger activation in the RCZ can possibly be seen as an indication of on-line fine-tuning of time-estimation behavior, which is stronger after positive feedback than after negative feedback[2]. In this way the activation is possibly comparable to the suggested role of the RCZ in the 'on-line adjustment of behavior to prevent errors' [30] and in post-error slowing [20, 21]. Magno et al. [30] used a visual search task with monetary incentive in which trials could be rejected to avoid losses and found that an area comparable to our RCZ was especially active during these reject trials. Hester et al. [20] and Klein et al. [21], on the other hand, found stronger activation in this area during post-error slowing.

The suggested relation between RCZ activation and fine-tuning behavior was more or less confirmed by the larger activation in the RCZ during negative feedback followed by correct adjustments, although this effect was only marginally significant. This was found in an analysis that directly compared negative feedback followed by either correct or incorrect adjustments, in which correct was defined as shortening the time-estimation when the estimation was too long (>1 s), or lengthening the estimation when the estimation was too short (<1 s)[3]. These

unexpected negative feedback, and in this way might lead to more activation in the RCZ. In this analysis we compared unexpected negative feedback (relatively good estimations followed by negative feedback) with expected negative feedback (relatively bad estimations followed by negative feedback), but found no significant differences in both a whole brain analysis and an ROI analysis. In the time-estimation task in its present form participants apparently do not build a strong expectation for the feedback they receive and therefore expectancy does not play a large role in the task that we have used.

2 An anonymous reviewer suggested that the size of change following positive feedback might be a good indication of whether the positive feedback is used to consolidate behavior. Indeed, we have found that positive feedback is followed by smaller changes in estimation time than negative feedback. We have performed an additional analysis of our imaging data to try to relate these changes in estimation time to BOLD signal changes. For this analysis we added the absolute size of change following a feedback stimulus as parametric modulation to our simplest model with the four different types of feedback. In this way we could compute the effect of change following a positive feedback stimulus on the BOLD response. We did, however, not find significant effects (positive or negative) of this modulation on the BOLD response. Possibly the changes are too noisy and random to quantify consolidation behaviorwithin subjects and the underlying systems in the brain.

3 An anonymous reviewer suggested that the actual size (in ms) of adjustment instead of the direction of adjustment would be a better measure for examining behavioral adjustments in the present task. In a separate analysis we performed a split-half analysis comparing trials with large adjustments with trials with small adjustments and could not find consistent results in brain areas of

trial-to-trial adjustments do not necessarily mean that our participants show learning behavior in the sense that performance improves over time. Our performance measures show that in our second run of 88 trials participants do not show better performance as compared to the first run in terms of more correct adjustments after negative feedback, better estimations in general, more or less change in estimation time following feedback or a smaller average interval in which the estimation was labeled as correct. Moreover, activation in the RCZ (data not shown) did not differ between the two blocks.

In addition to the difference in the RCZ we found that the pre-SMA was more strongly activated after negative feedback followed by a correct adjustment than after negative feedback followed by an incorrect adjustment. This more strongly activated pre-SMA is in accordance with Fiehler et al. [31], who reported a more strongly activated pre-SMA following errors that were corrected compared to errors that were not corrected. Furthermore, this additional activation might also be related to the additional activation to stimuli followed by a task switch as compared to stimuli followed by a repetition that was reported by Rushworth et al. [32]. Finally, it fits the observations of Shima et al. [33], who found that the pre-SMA was more activated in monkeys, whenever they had to set aside the current motor plan and come up with a new plan for the following movements. The activation in the pre-SMA can therefore be seen as a marker for behavior ranging from subtle fine-tuning of behavior to abrupt changes in behavioral strategy.

Additional activation to negative feedback followed by correct adjustments was also found in the left inferior parietal cortex and left dorsolateral prefrontal cortex. These areas have been found in numerous studies comparing stimuli that require more or less demanding processing, and have been related to executive function in a working memory framework (e.g. [34, 35]). The finding that only left parietal and prefrontal areas were involved can possibly be explained by the findings of Coull and Nobre [36] who showed that temporal orienting is lateralized to the left as compared to spatial orienting. In the current task the temporal orienting is of key importance and therefore correct adjustments most likely have to be preceded by stronger temporal orienting. They also showed that especially an area overlapping with our parietal area is involved in this type of orienting.

In contrast to the positive relation between activation in areas involved in high level processing with flexibility, activation in areas that are more important for the low-level basic processing of the feedback stimuli (amygdala and fusiform gyrus) was negatively correlated with estimation performance and to a lesser extent also with flexibility. Participants with relatively strong activations in these areas were more likely to show worse performance. Possibly, more extensive low-level processing of the feedback stimuli can be seen as a distracting factor. Being involved in the processing of either the visual characteristics or the emotional content of the feedback stimulus might be distracting from the higher level

interest. Therefore we decided not to include this analysis and focus on the analyses described in the Results section.

goals of the task.
An interesting finding was that positive feedback stimuli activated the amygdala more strongly. We hypothesized that faces and especially fearful faces would show stronger activation in the amygdala, based on many previous studies that showed a strong amygdala response to fearful faces whether they were attended or not [37]. Facial feedback stimuli were accompanied by stronger amygdala activation than verbal feedback stimuli, but positive feedback more strongly activated the amygdala, irrespective of feedback modality. Previous studies using this task did not report this stronger amygdala activation [12, 13], but unpublished data of our own group shows that this effect is consistent over different types of positive feedback in the time-estimation paradigm. Possibly the previous studies missed this effect due to the inclusion of fewer participants and the relative closeness of this amygdala activation to more strongly activated areas in the striatum. The finding is in line with studies that have suggested a role for the amygdala in reward processing (for a review see Murray [38]). Our findings show that the context in which the faces are presented and their role as negative and positive feedback are more important than their intrinsic emotional value with respect to activating the amygdala.
To conclude, the present findings showthat in the current context of highly unpredictable feedback, activation in the RCZ is not necessarily related to worse than expected outcomes as predicted by the reinforcement learning theory. On the other hand, it could be confirmed that activation in this area, and other areas involved in higher order cognitive processes, is related to behavioral adjustments as was shown by different analyses relating better performance to higher brain activity in these areas. So, these findings are in line with a role for the RCZ in remedial action as suggested by the reinforcement learning theory, but activation in this area does not necessarily reflect worse than expected outcomes. Our paradigm provides an example of how unpredictable and equiprobable feedback stimuli in combination with sophisticated measures of remedial action can be assessed to further unravel the role of the RCZ in feedback processing and remedial action.

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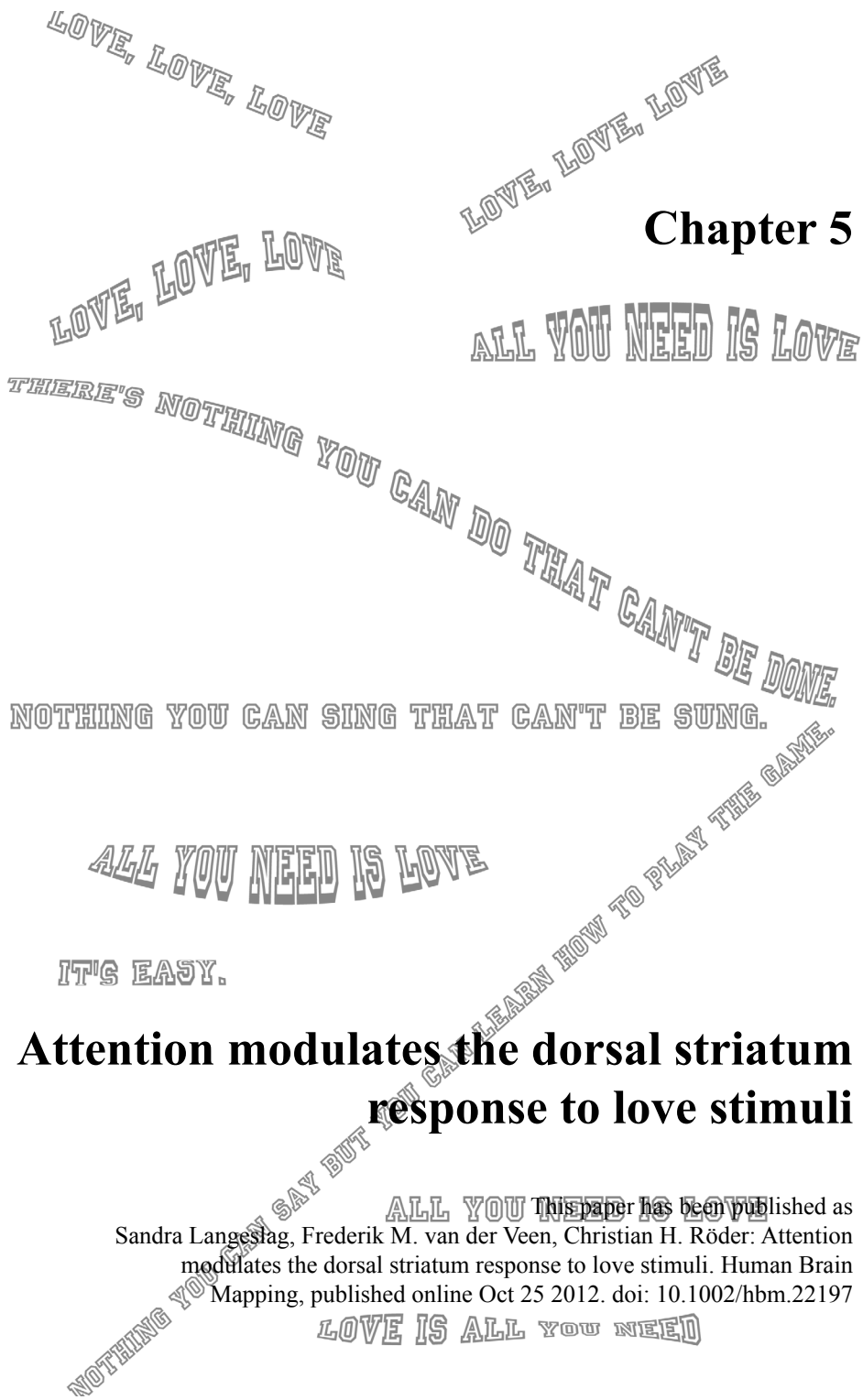

Chapter 5

Attention modulates the dorsal striatum response to love stimuli

This paper has been published as
Sandra Langeslag, Frederik M. van der Veen, Christian H. Röder: Attention modulates the dorsal striatum response to love stimuli. Human Brain Mapping, published online Oct 25 2012. doi: 10.1002/hbm.22197

Abstract

In previous functional magnetic resonance imaging (fMRI) studies concerning romantic love, several brain regions including the caudate and putamen have consistently been found to be more responsive to beloved-related than control stimuli. In those studies, infatuated individuals were typically instructed to passively view the stimuli or to think of the viewed person. In the current study, we examined how the instruction to attend to, or ignore the beloved modulates the response of these brain areas. Infatuated individuals performed an oddball task in which pictures of their beloved and friend served as targets and distractors. The dorsal striatum showed greater activation for the beloved than friend, but only when they were targets. The dorsal striatum actually tended to show less activation for the beloved than the friend when they were distractors. The longer the love and relationship duration, the smaller the response of the dorsal striatum to beloved-distractor stimuli was. We interpret our findings in terms of reinforcement learning. By virtue of using a cognitive task with a full factorial design, we show that the dorsal striatum is not activated by beloved-related information per se, but only by beloved-related information that is attended.

Introduction

The lifetime prevalence of romantic love is extremely high, as romantic love strikes nearly 100% of the people at one or more times during their life. As a comparison, the lifetime prevalence of experiencing any mental disorder is 'only' 46.4% (National Institute of Mental Health, US). In addition, when people fall in love, it affects their lives to a great extent: People are often willing to change their clothing, hobbies, friends, job, country or even their religion to be able to be together with their beloved [1]. It may be clear that the phenomenon of romantic love requires thorough scientific investigation. In the last decade, the scientific community has begun to study how the brain processes beloved-related information differently from other information.

In previous functional Magnetic Resonance Imaging (fMRI) studies, participants viewed pictures of the face of the beloved, while pictures of the faces of friends or acquaintances, erotic pictures, autobiographical pictures, pictures of landscapes, and/or verbal or arithmetic tasks typically served as control stimuli [2-10]. Participants were either instructed to passively view the stimuli, or to think of the viewed person. Differences between these studies include the populations studied, such as individuals who had fallen in love only recently [3] or longer ago [2, 4], individuals who had a beloved of the same or the opposite sex [10], individuals who were happily or unhappily in love [5, 7], and individuals from Western or Eastern cultures [8], as well as the inclusion of pain conditions [9]. In another fMRI study [11], the name of the beloved, the name of a friend, and a word that described a passion of the participants were presented as subliminal primes in a lexical decision task. Despite these differences between studies, a number of brain areas have shown increased activation in response to beloved-related information compared to control information in multiple studies, including the caudate, putamen, ventral tegmental area (VTA), insula, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and inferior frontal gyrus (IFG). It is not obvious, though, how to interpret the observed activation for beloved-related stimuli, as there is no one-to-one mapping between brain regions and their functions. For example, the caudate and putamen form the dorsal striatum that has been implicated in the control of movement, cognitive functions, and reward-related processing [12].

There is no doubt that the above-mentioned pioneering studies have yielded valuable knowledge. Now the time has come to take the scientific investigation of the neurocognition of romantic love to the next level by examining the processing of beloved-related information during cognitive tasks, employing full factorial designs. The advantages of this approach are threefold. First, the use of well-established tasks helps to interpret the brain response in terms of cognitive operations. Second, the resulting behavioral data may aid in interpreting the neural findings. Finally, the use of full factorial designs allows for both main and interaction effects to be studied [13], which sheds light on the context-dependence of effects.

Beloved-related stimuli obviously are highly emotional and motivationally rele-

vant for the infatuated individual. It is well known that attention is increased for emotional over neutral stimuli [14]. In an event-related potential (ERP) study, in which infatuated individuals passively viewed pictures of their beloved, a friend, and a beautiful stranger, the late positive potential (LPP/P3) was increased in response to the beloved. In line with the notion that the LPP/P3 reflects motivated attention [15], it was concluded that romantic love is associated with increased attention for the beloved [16]. In a subsequent ERP study, in which infatuated individuals performed a full factorial oddball task with pictures of the beloved and friend as target and distractor stimuli, it was shown that this increased attention for the beloved occurred even when the participants were explicitly instructed to ignore the beloved and to pay attention to the friend instead [17]. In the current fMRI study, we used the same full factorial oddball task to examine how the instruction to attend to, or ignore the beloved modulates the BOLD response in brain regions that are sensitive to beloved-related information.

Some previous fMRI studies concerning romantic love included an attentional task that did not involve any beloved-related stimuli, as an implicit baseline or as an explicit control condition [2, 3, 9]. The results of those studies are hence controlled for the general effects of paying attention to the task at hand. But because these attentional tasks did not involve beloved-related information, they did not elucidate how attention modulates the processing of beloved-related information. Although the oddball task has not been used in previous fMRI studies regarding romantic love, it has been used in previous fMRI studies regarding emotion or reward. In most of those studies the emotional or motivational salience of the stimuli was varied within one task condition (i.e. targets or distractors) only [18-27]. In one study, the emotionality of the stimuli was varied within the target condition in one group, and between the target and distractor conditions in another group of participants [28]. To our knowledge no previous emotion or reward fMRI studies have used an oddball task with a full factorial design, and the current study could thus also inform future emotion and reward studies.

Material and methods

Particpants

Twenty students of the Erasmus University Rotterdam participated in this study. Five of these participants had to be excluded due to scanner malfunction (n = 2), loss of stimulus timing files (n = 2), and excessive head movement (n = 1). Thus, the analyses were based on 15 participants (6 men; mean age = 20.8 yrs, range = 18-25). Only participants who had been in love (in Dutch: "verliefd", meaning 'in love' or 'infatuated') for a relatively short period of time (less than nine months) and who's beloved was of the opposite sex were included. Other inclusion criteria were normal or corrected-to-normal vision, no medical diagnosis, no use of medication known to affect the central nervous system, and no fMRI contraindications. All participants were right-handed as determined by a hand preference questionnaire [29]. A questionnaire score of -10 reflects extreme left-handedness

while a score of 10 reflects extreme right-handedness, and all participants had a score of 7 or higher. The study was approved by the ethics committee of the Erasmus Medical Center, Rotterdam and was conducted in accordance with the Declaration of Helsinki. Participants provided written informed consent prior to testing and were remunerated with course credit or 20 euros.

Procedure

To start with, participants rated the extent to which they experienced romantic love with the beloved on a 9-point Likert scale (1 = not in love at all, 9 = very much in love) (i.e. love intensity). Then, participants indicated for how many months (1 week = 0.25 month) they had been in love (i.e. love duration), and whether they were involved in a romantic relationship with their beloved. If they were, they indicated for how many months (1 week = 0.25 months) they had been involved in a romantic relationship with their beloved (i.e. relationship duration). The participants also completed the Dutch version of the Passionate Love Scale (PLS) [16, 17], which assesses the extent to which someone experiences passionate or romantic love [30], (minimum mean score = 1, maximum = 9; Chronbach's alpha = .93).

The stimuli were photographs of the faces of the participants' beloved and friends, and of a person that was unknown to them. A friend was defined as someone of the same sex as the beloved that the participant knew well, but for whom they had no romantic feelings. The photographs of the beloved and friend were supplied by the participants and were digitally adjusted to meet the requirements of the experiment (grey-scale, showing face only). The male participants viewed only female faces, whereas the female participants viewed male faces (i.e. the beloved, friend and the unknown person were of the opposite sex). A separate sample of ten participants (5 men; mean age = 23.5 yrs, range = 18-28) who did not know people in the photographs and were unaware of the purpose of the study rated the attractiveness of the faces and the quality of the images on 9-point Likert scales (1 = very unattractive/poor quality, 9 = very attractive/high quality). The mean attractiveness ratings were 4.9 (SD = 0.3) for the beloved, 4.6 (SD = 0.3) for the friends, and 4.7 (SD = 0.6) for the unknown persons. Attractiveness did not differ between conditions, $F(2,18) = 1.8$, $\varepsilon = .77$, $p = .20$. The mean image quality ratings were 5.4 (SD = 0.8) for the beloved, 5.3 (SD = 0.8) for the friends, and 5.0 (SD = 2.0) for the unknown persons. Image quality did not differ between conditions, $F(2,18) < 1$, ns.

In the oddball task, a trial consisted of the presentation of a fixation cross with jittered duration between 1550 and 2050 ms, followed by the presentation of a face for 250 ms, with no inter-trial interval. The face of the unknown person always served as the standard stimulus, occurring in 80% of the trials. The faces of the beloved and friends each appeared pseudo randomly in 10% of the trials, and were separated by three to five standard stimuli.

Participants performed a few practice trials outside the scanner. Inside the scan-

ner the participants completed four experimental runs, which consisted of 200 trials each. In two of the runs, the beloved was the target stimulus and the friend was the distractor. In the other two runs, the friend was the target and the beloved was the distractor, making the design full factorial. These run types alternated and run order was counterbalanced across participants. Participants were instructed to respond to the target stimulus by pressing a button with their right thumb. Accuracy was stressed over speed.

fMRI recording and signal processing

The MRI scans were acquired on a 3T scanner (General Electric, Milwaukee, USA). Functional images were obtained using echo-planar imaging sequences (EPI) in four runs of 210 volumes each. At the beginning of each run, five dummy volumes were acquired but not stored, to allow for T1-equilibration effects. The T2*-weighted images were acquired in 26 axial slices (thickness = 3.5 mm, interslice gap = 0.5 mm) with a repetition time (TR) of 2000 ms, echo time (TE) of 30 ms, field of view (FOV) of 220 mm, voxels of 1.72 × 1.72 × 3.50 mm, and sequential slice acquisition order from superior to inferior. For anatomical reference, a 3D high resolution inversion recovery fast spoiled gradient recalled echo T1-weighted sequence was collected, covering the whole brain in 192 slices (thickness = 1.6 mm, overlap = 0.8 mm) with a FOV of 250 mm, and voxels of 0.49 × 0.49 × 0.80 mm.

The data were preprocessed using Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/) [31]. Six-parameter rigid-body motion correction within and across runs was performed using Fourier interpolation [32] such that all volumes were spatially registered to the volume acquired closest in time to the particular participant's anatomical volume. In three participants, the third and fourth runs were excluded from further analysis because of excessive head movement (i.e. more than 3 mm in the x, y, or z direction). To account for the timing offset between slices, slice timing correction was performed using Fourier interpolation such that all slices were realigned to the first slice of the associated volume. To normalize the functional data to Talairach space [33], initially each subject's high-resolution anatomical volume was spatially registered to the so-called TT_N27 template (in Talairach space) using a 12-parameter affine transformation; the same transformation was then applied to the functional data. All volumes were spatially smoothed using a Gaussian filter with a full-width at half maximum of 6 mm. Finally, the signal intensity of each voxel was scaled to a mean of 100.

Statistical analyses

Hit (i.e. proportion button presses for target stimuli) and false alarms rates (i.e. proportion button presses for distractor stimuli) were computed using the correction recommended by Snodgrass and Corwin [34]. These data, as well as the median response times (RTs) for hits, were analyzed with repeated measures

analyses of variance (rmANOVA) with the factor Love (beloved, friend) using a significance level of 5%. Only significant effects are mentioned.
Single-subject fMRI analyses were performed using AFNI. There were four event types of interest, namely beloved-target, beloved-distractor, friend-target, friend-distractor, and a nuisance event type that included all incorrect trials. Constant, linear, and quadratic terms were included for each run separately (as regressors of no interest) to model the baseline and drifts of the MR signal. Correct standard trials were not modeled explicitly and constituted the implicit baseline in the model. Therefore, all parameter estimates reported in this study are with respect to correct standard trials as a baseline. Because we did not want to assume the shape of the BOLD response, responses were estimated from stimulus onset until 14 sec after stimulus onset via a deconvolution model using cubic spline basis functions. Because the estimated BOLD response averaged across subjects peaked around 4 to 6 sec after stimulus onset, see Fig. 1, the BOLD response averaged over the third and fourth time points (i.e. 4-6 sec) after stimulus onset was fed into the group-level analyses.
We focused our group-level analysis on a set of regions-of-interest (ROIs) that have been found to be activated more to beloved-related than control stimuli in previous studies [2-8, 10], as discussed in the introduction. Six bilateral anatomical ROIs were selected using the Talairach-Tournoux Atlas in AFNI: caudate, putamen, insula, ACC, PCC, and IFG, see Fig. 1. An ROI that included the VTA was defined using the ventral diencephalon region of the DD_Desai_MPM atlas in AFNI, see Fig. 2. For each ROI and condition, the voxel-wise betas were averaged in order to get one beta per condition per ROI. For each ROI, the beta values were entered into a 2x2 rmANOVA with the factors Love (beloved, friend) and Task (target, distractor), which was performed with SPSS 18. Because pre-

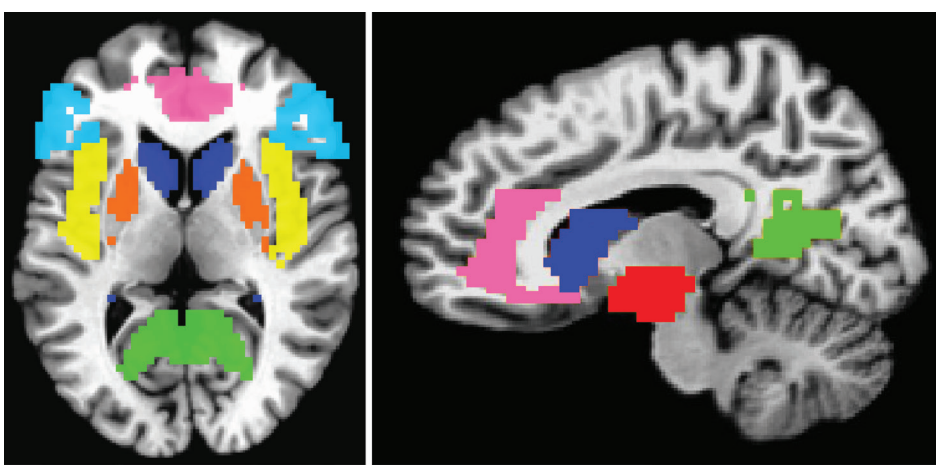

Fig 1. The seven bilateral ROIs at z = 7 (left panel) and x = -10 (right panel). Dark blue = caudate, orange = putamen, red = VTA, yellow = insula, pink = ACC, green = PCC, light blue = IFG

liminary analyses including the factor Hemisphere (left, right) did not reveal any significant interactions involving both the factors Love and Hemisphere, all ps > .10, activity was collapsed across hemispheres. In the Supporting Information, we present analyses for the left and right ROIs separately. A significance level of 5% was selected and significant Love x Task interactions were clarified by paired-samples t-tests.

For completeness, we also report the results of a whole-brain voxel-wise (excluding white matter voxels) 2x2 rmANOVA with the factors Love (beloved, friend) and Task (target, distractor). A combined uncorrected threshold of $p < .001$ at the voxel level and a minimum cluster size of 25 voxels was used, which resulted in a corrected significance level of 5% as determined by the 3dClustSim program in AFNI.

Results

Love characteristics

The mean duration of the participants' romantic love was 5.1 months (SD = 1.6, range = 2.5-8.0). All but one female participant were involved in a romantic relationship with their beloved and the mean duration of these relationships was 3.9 months (SD = 1.7, range = 1.0-6.5). The participants' mean self-reported love intensity was 7.9 (SD = 1.0, range = 6-9) and their mean PLS score was 7.2 (SD = 0.9, range = 5.1-8.8).

Behavioral data

Mean accuracy on the oddball task was very high, namely 98% (range = 92-100), which indicates that participants were alert and adhered to the instructions. Hit rates did not differ significantly between the beloved-target (M = .98, SD = .02) and the friend-target (M = .96, SD = .07) conditions, $F(1,14) = 1.4$, $p = .25$. False alarm rates, however, were higher in the beloved-distractor (M = .05, SD = .04) than in the friend-distractor (M = .03, SD = .02) condition, $F(1,14) = 7.5$, $p = .016$. Also, RTs tended to be shorter for beloved-target (Mdn = 528 ms, SD = 64) than for friend-target (Mdn = 561 ms, SD = 80) stimuli, $F(1,14) = 3.6$, $p = .079$.

ROI analyses

See Fig. 2 for the BOLD responses at 0 to 14 sec after stimulus onset to the four stimulus types in each ROI, and see Table 1 for the results of the 2x2 rmANOVA on the average BOLD response at 4-6 sec after stimulus onset. None of the ROIs displayed a significant main effect of Love. In the putamen, the Love x Task interaction was significant. The average responses at 4-6 sec after stimulus onset in the putamen are displayed in Fig. 3. The BOLD response was significantly larger for the beloved-target than for the friend-target stimuli, $t(14) = 3.0$, $p = .010$. The response was smaller for beloved-distractor than friend-distractor stimuli, but this difference did not reach significance, $t(14) = -1.9$, $p = .076$. Furthermore, the response was significantly larger for beloved-target than for beloved-distractor

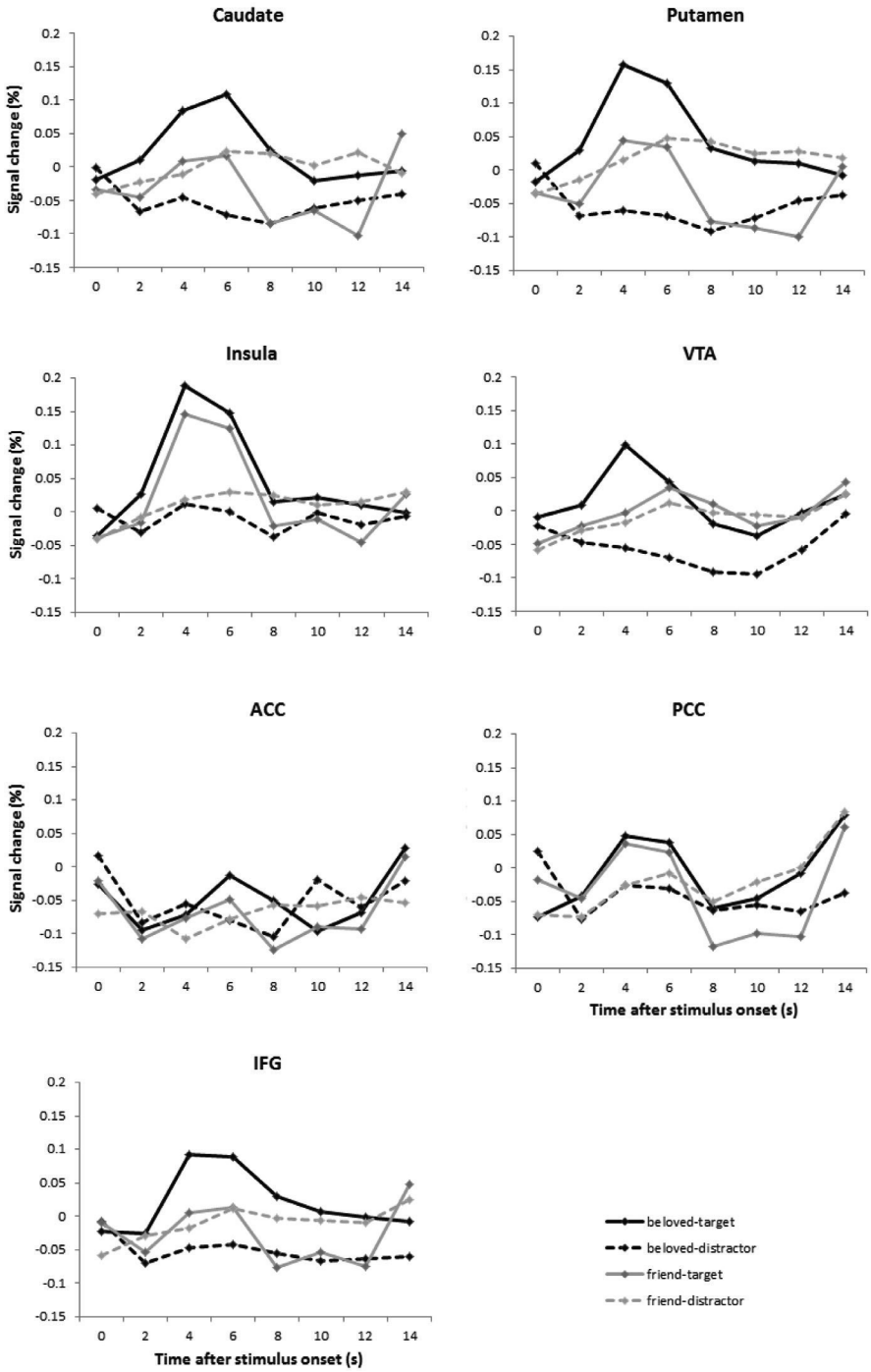

Fig 2. Estimated BOLD responses to the four event types of interest compared to the baseline (i.e. correct standard trials) in the seven bilateral ROIs

stimuli, $t(14) = 4.7$, $p < .001$, while the responses for friend-target and friend-distractor stimuli did not differ, $t(14) = 0.2$, $p = .87$.
The caudate, VTA, and IFG showed the same activation pattern as the putamen, see Fig. 1. The Love x Task interaction was not significant in the VTA or IFG though, and only approached significance in the caudate. When subdividing the caudate into its head, body, and tail using the Talairach-Tournoux Atlas in AFNI, trends towards significant Love x Task interactions were observed in the head, $F(1,14) = 3.5$, $p = .081$, and body, $F(1,14) = 3.7$, $p = .076$, but not in the tail, $F(1,14) < 1$, ns.
The main effect of Task was highly significant in the caudate, putamen, VTA, insula, and IFG, with the responses being larger for target than distractor stimuli, see Fig. 2.

Correlational analyses
Next, we examined whether the observed differences between conditions in putamen response were associated with the love intensity, the mean PLS score, and the duration of the romantic feelings. The variables love duration and rela-

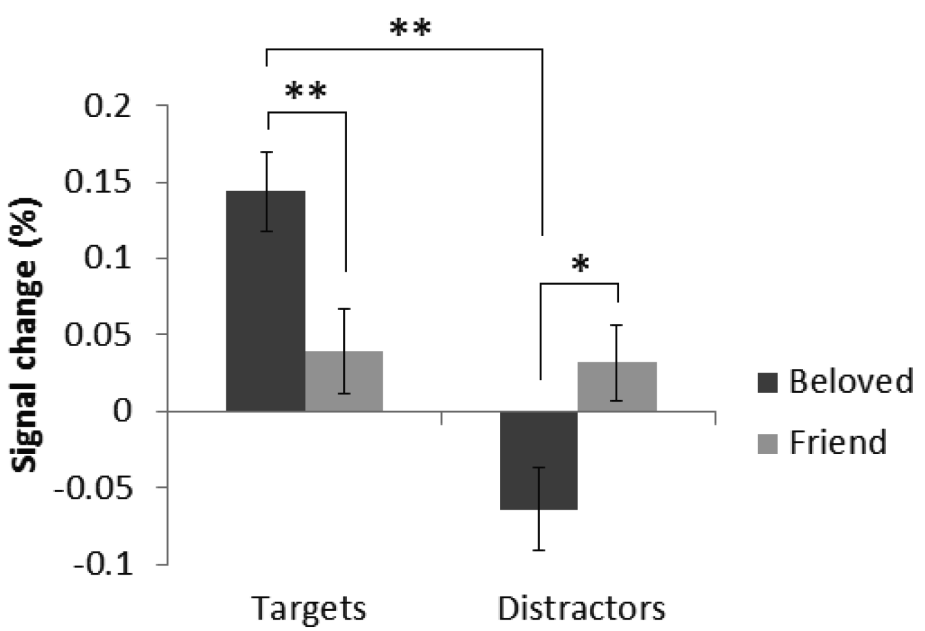

Fig. 3 Average percent signal change in putamen at 4-6 sec after stimulus onset for each of the four stimuli types compared to the baseline (i.e., standard correct trials). The BOLD response was significantly larger for beloved-target than for friend-target and beloved-distractor stimuli, which is indicated by the double asterisks. The BOLD response tended to be smaller for beloved-distractor than for friend-distractor stimuli, which is indicated by the single asterisk.

tionship duration were highly correlated, r(12)= .86, p < .001. To increase statistical power, we used the average of the two in these correlational analyses. Pearson correlation coefficients between the love characteristics (i.e. love intensity, mean PLS score, and the average between love and relationship duration) and the beta values foreach of the four contrasts were computed. Neither love intensity, nor mean PLS score correlated significantly with the beta values of any of the contrasts, -.29 < all rs(13) < .41, all ps > .13. The putamen response between beloved-distractor and friend-distractor, r(13) = -.72, p = .003, between beloved-target and beloved-distractor, r(13) = .59, p = .020, and between friend-target and friend-distractor, r(13) = -.66, p = .008. To clarify these findings, Pearson correlation coefficients were computed between the average between love and relationship duration and the putamen response in each of the conditions. The average between love and relationship duration was negatively correlated with the putamen response to beloved-distractor stimuli, r(13) = -.59, p = .022, and

Table 1 Overview of the results of the 2x2 rmANOVAs on the average BOLD signal at 4-6 sec after stimulus onset in the seven bilateral ROIs

ROI	Main effect of Love	Main effect of Task	Love x Task interaction
Caudate	F(1,14) < 1, ns	F(1,14) = 43.3, p < .001*	F(1,14) = 3.7, p = .073
Putamen	F(1,14) < 1, ns	F(1,14) = 40.8, p < .001*	F(1,14) = 6.6, p = .022*
VTA	F(1,14) < 1, ns	F(1,14) = 9.4, p < .008*	F(1,14) = 2.3, p = .16
Insula	F(1,14) < 1, ns	F(1,14) = 76.6, p < .001*	F(1,14) < 1, ns
ACC	F(1,14) = 3.3, p = .089	F(1,14) = 3.1, p = .10	F(1,14) < 1, ns
PCC	F(1,14) < 1, ns	F(1,14) = 3.8, p = .071	F(1,14) < 1, ns
IFG	F(1,14) < 1, ns	F(1,14) = 24.4, p < .001*	F(1,14) = 2.1, p = .17

* = significant

Table 2 Location and Talairach coordinates for the peak voxel of significant clusters for the main effect of Task (p < 0.05 corrected) at 4-6 sec after stimulus onset in the whole-brain analysis. All of these clusters showed a greater BOLD response for target than distractor stimuli.

Region	**x**	**y**	**z**	**F(1,14)**
Left postcentral gyrus	49	31	50	190.9
Right culmen	-10	52	-15	107.3
Left middle occipital gyrus	49	64	-3	84.5
Right middle frontal gyrus	-43	-40	11	80.1
Left culmen	22	52	-18	28.1
Left middle frontal gyrus	28	-37	26	46.1
Right precuneus	-16	67	38	26.0
Left cuneus	13	76	35	24.7

positively correlated with the response to friend-distractor stimuli, $r(13) = .69$, $p = .005$, but not significantly correlated with beloved-target stimuli, $r(13) = .29$, $p = .29$, or friend-target stimuli, $r(13) = -.34$, $p = .21$. To summarize, the longer the love and relationship duration, the smaller the putamen response to beloved-distractor stimuli and the larger the putamen response to friend-distractor stimuli.

Whole-brain analyses

In the whole-brain analysis, no significant clusters appeared for the main effect of Love, or for the Love x Task interaction. See Table 2 for the eight significant clusters for the main effect of Task. The largest of these clusters extended anterior and posterior of the left central sulcus. All of these clusters showed a larger response for target than distractor stimuli.

Discussion

The goal of this study was to examine how the instruction to attend to, or ignore the beloved modulates the BOLD response in brain regions that are sensitive to beloved-related information. To this end, infatuated participants performed an oddball task in which pictures of the faces of their beloved and friend served as target and distractor stimuli alternately.

We focused our analysis on brain areas that have consistently been shown to be more responsive to beloved-related information than control information in previous fMRI studies: the caudate, putamen, VTA, insula, ACC, PCC, and IFG [2-8, 10, 11]. In the current study, none of these brain regions was differentially activated in response to the beloved compared to friend stimuli when collapsing across target and distractor conditions. Only when the beloved and friend stimuli were targets, the dorsal striatum showed greater activation for beloved compared to friend stimuli. In many previous studies, increased dorsal striatum activation for beloved compared to control stimuli has been observed [2-5, 10, 11]. In most of those studies, no cognitive task was associated with the beloved and control stimuli, which were presented in a blocked design with relatively long stimulus durations. We show that increased dorsal striatum activation for beloved-related information can also be observed during an event-related cognitive task with very short stimulus durations.

Although dorsal striatum activation was increased for beloved-related information when it was attended, the responses of the dorsal striatum for beloved-distractor and friend-distractor stimuli did not differ significantly. If anything, the dorsal striatum was actually less responsive to beloved compared to friend stimuli when they were distractors. By virtue of the full factorial design, the current study extends existing knowledge from previous studies by showing that the dorsal striatum is not activated by beloved-related information per se, but only by beloved-related information that is attended.

Because in some previous studies the activation by beloved-related information was unilateral rather than bilateral [2, 3], we presented additional analyses sep-

arately for the left and right ROIs as Supporting Information. The only difference with the bilateral analyses was that the Love x Task interaction additionally reached significance in the left caudate, particularly in the left caudate body. In many previous studies, beloved-related information has activated bilateral putamen [2, 4, 5] and bilateral caudate [4, 10], and in those studies in which unilateral caudate activation was observed it was mostly right-lateralized [2, 3, 11] as opposed to left-lateralized in the current study. It is as of yet unclear what causes the lateralization of the caudate response to (attended) beloved-related information, and this intriguing issue deserves further investigation.

The dorsal striatum is highly heterogeneous in terms of connectivity and functionality, which gives it the ultimate position to influence goal-directed behavior by integrating information regarding cognition, motivation, and motor control [12, 35]. In a previous study, caudate activation was specifically associated with the amount of obsessive thinking about the beloved [2]. It has also been suggested that the caudate plays a role in the attentional aspects of romantic love [3], and the current results support this suggestion. Generally, the increased dorsal striatum response to attended beloved-related stimuli in the current and previous studies fits the notion that romantic love is a motivational state that is associated with approach behavior [2, 3, 36].

While the ventral striatum has been associated with reward anticipation, the dorsal striatum is more involved in using reward outcomes to guide future cognitions and actions [37], including social behavior, with the goal to maximize the reward obtained [35]. The dorsal striatum has specifically been implicated in reinforcement learning [12, 38], which entails that previously rewarded behavior is likely to be repeated while previously punished behavior is not. It has been shown that gambling actions that were in accordance with reinforcement learning activated the dorsal striatum more than gambling actions that were in conflict with reinforcement learning [39]. The currently observed increased dorsal striatum activation for the beloved stimuli that were targets resonates with the notion that attending/responding to one's beloved is associated with positive reinforcement more than attending/responding to one's friend, or ignoring one's beloved is. Interestingly, the BOLD response in the dorsal striatum to beloved stimuli that were distractors was smaller in participants who had fallen in love with their beloved longer ago and who had been in a romantic relationship with their beloved for a longer time. The association between the BOLD response in the dorsal striatum to friend stimuli that were distractors showed the opposite pattern, with larger responses in participants that had fallen in love and had become involved in a relationship longer ago. The association between the response of the dorsal striatum and the duration of the romantic love supports our interpretation of the dorsal striatum response as reflecting prior reinforcement of social actions.

This reinforcement learning would lead infatuated individuals to preferentially pay attention to their beloved, perhaps at the cost of paying attention to their friend. Correspondingly, the participants in the current study tended to respond

faster to their beloved than to their friend. Also, the increased false alarm rate for the beloved indicates that infatuated individuals find it harder to ignore their beloved than to ignore their friend. These behavioral findings corroborate the ERP-based conclusion that romantic love is associated with increased attention for the beloved [16, 17].

The current study has a couple of limitations. First, because the dorsal striatum plays a role in motor functions [35], our findings could be confounded by the motor responses. We feel confident though that the responses of the dorsal striatum do not reflect the button presses, because no difference was observed between the dorsal striatum responses for friend-target and friend-distractor stimuli, even though the former were associated with button presses and the latter were not. Second, given the known gender differences in romantic love [40-43], it would have been interesting to examine gender differences in the current study. Unfortunately, the inclusion of only six men in our data analyses rendered the examination of gender differences unfeasible. Third, the mask that was used to extract the signal from the VTA contained the entire ventral diencephalon instead of just the VTA. Although the VTA is a small region, the limited spatial resolution of fMRI combined with spatial resampling and spatial smoothing during preprocessing justifies the use of a larger mask. Nevertheless, the use of this larger mask may have limited the power to observe a significant main effect of Love or a Love x Task interaction. Future studies could focus on the VTA by scanning only a part of the brain with higher resolution.

The oddball task used in the current study was adapted from a previous ERP study [17]. In that study, it was observed that the LPP/P3 was larger for target compared to distractor stimuli, which reflected task-related attention. This main effect of Task in the ERP was very robust, and so was main effect of Task in the current study. Many brain areas showed an increased response to targets compared to distractors, including a large cluster extending anterior and posterior of the central sulcus of the left hemisphere, which obviously reflects the required button presses for the target stimuli. In the prior ERP study, the LPP/P3 also showed a main effect of Love, being larger for beloved compared to friend stimuli, reflecting love-related attention. The target-related LPP/P3 for visual stimuli is thought to emerge from a widespread network including the parietal, temporal, and cingulate cortices [44], and it has been shown that the emotional modulation of the LPP/P3 originates in the prefrontal, occipital, parietal, and temporal cortices [45, 46]. In the current study, no main effects of Love occurred in the ROI or whole-brain analyses. The former may be due to the fact that involvement in the LPP/P3 was not an ROI selection criterion, and the latter may be due to reduced power in the whole-brain analysis. In the previous ERP study, the LPP/P3 did not display a Love x Task interaction. Signals from certain neural populations, such as those oriented tangentially to the scalp, with closed field configurations, and located in subcortical areas, are not reflected in the ERP signal [47]. The currently observed Love x Task interaction in the subcortical dorsal striatum could thus not

have been observed in the ERP. It may be clear that ERP and fMRI studies yield different types of information, and that both modalities are valuable when trying to elucidate the neurocognition of romantic love.

It is known that reward and motivation modulate attention [48-50], but less is known about how attention modulates reward processing. The current study raises the question to what extent the current findings are generalizable to other types of reward processing. On the one hand, it may be that attention modulates the dorsal striatum response to any kind of reward stimuli. This hypothesis may be tested using a similar full factorial oddball task with reward stimuli other than pictures of the beloved, such as drug-related or sexual stimuli, or monetary gains or losses. On the other hand, the current correlational analyses suggest that it is (social) reinforcement learning instead of attention per se that may be the key factor in modulating the dorsal striatum response to reward stimuli. More research is needed to clarify the roles of attention and reinforcement learning on the processing of beloved-related information, and on reward processing in general. It will remain important to disentangle the effects of reward and attention on neural processing, as they are often confounded [51, 52].

To conclude, we present here the first fMRI study in which the neurocognition of romantic love is studied using a cognitive task with a full factorial design. We show that the dorsal striatum responds preferentially to beloved-related information only when it is attended. We explain this finding by interpreting the dorsal striatum response as reflecting previous reinforcement of social actions. This study greatly advances our understanding of the role of the dorsal striatum in romantic love. More research is needed to further elucidate the roles of the multiple brain regions that are activated by beloved-related information.

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Supplementary Material

ROI analyses separately for the left and right ROIs

See Table s1 for the results of the 2x2 rmANOVA on the average BOLD response at 4-6 sec after stimulus onset for the left and right ROIs separately. None of the left or right ROIs displayed a significant main effect of Love. In the left caudate and the left and right putamen, the Love x Task interaction was significant. The pattern of results was the similar between these three regions. The response was significantly larger for the beloved-target than for the friend-target stimuli, all ps < .041. The response tended to be smaller for beloved-distractor than friend-distractor stimuli, but these differences did not reach significance, all ps < .093. The response was significantly larger for beloved-target than for beloved-distractor stimuli, all ps < .002. The responses for friend-target and friend-distractor did not differ, all ps > .60.

When subdividing the left and right caudate into their heads, bodies, and tails using the Talairach-Tournoux Atlas in AFNI, a significant Love x Task interaction was observed in the left caudate body only, see Table s2. Post hoc comparisons again showed the same pattern of results. The response was significantly larger for the beloved-target than for the friend-target stimuli, p = .031. The response tended to be smaller for beloved-distractor than friend-distractor stimuli, but this difference did not reach significance, p = .076. The response was significantly larger for beloved-target than for beloved-distractor stimuli, p = .001. The responses for friend-target and friend-distractor did not differ, p = .95.

Table s1. Overview of the results of the 2x2 rmANOVAs on the average BOLD signal at 4-6 sec after stimulus onset in the seven ROIs for each hemisphere separately

ROI	Hemi	Main effect of Love	Main effect of Task	Love x Task interaction
Caudate	Left	F(1,14) < 1, ns	F(1,14) = 52.8, p < .001*	F(1,14) = 5.1, p = .040*
	Right	F(1,14) < 1, ns	F(1,14) = 32.3, p < .001*	F(1,14) = 2.7, p = .12
Putamen	Left	F(1,14) < 1, ns	F(1,14) = 50.2, p < .001*	F(1,14) = 5.3, p = .037*
	Right	F(1,14) < 1, ns	F(1,14) = 29.5, p < .001*	F(1,14) = 7.7, p = .015*
VTA	Left	F(1,14) < 1, ns	F(1,14) = 12.3, p = .003*	F(1,14) = 2.8, p = .12
	Right	F(1,14) < 1, ns	F(1,14) = 6.5, p = .023*	F(1,14) = 1.5, p = .24
Insula	Left	F(1,14) < 1, ns	F(1,14) = 73.1, p < .001*	F(1,14) < 1, ns
	Right	F(1,14) < 1, ns	F(1,14) = 70.7, p < .001*	F(1,14) < 1, ns
ACC	Left	F(1,14) = 2.1, p = .17	F(1,14) = 2.9, p = .11	F(1,14) < 1, ns
	Right	F(1,14) = 4.2, p = .060	F(1,14) = 3.0, p = .10	F(1,14) < 1, ns
PCC	Left	F(1,14) < 1, ns	F(1,14) = 2.9, p = .11	F(1,14) < 1, ns
	Right	F(1,14) < 1, ns	F(1,14) = 4.2, p = .060	F(1,14) < 1, ns
IFG	Left	F(1,14) < 1, ns	F(1,14) = 7.9, p = .014*	F(1,14) = 2.7, p = .12
	Right	F(1,14) = 1.1, p = .32	F(1,14) = 37.7, p < .001*	F(1,14) = 1.3, p = .27

* = significant

The main effect of Task was significant in the left and right caudate, putamen, ventral tegmental area, insula, and inferior frontal gyrus, with the responses being larger for target than distractor stimuli.

Correlational analyses separately for the left and right ROIs

Pearson correlation coefficients between the love characteristics (i.e. love intensity, mean PLS score, and the average between love and relationship duration) and the beta values for each of the four contrasts in the left caudate and left and right putamen were computed. Neither love intensity, nor mean PLS score correlated significantly with the beta values of these contrasts in any of the three ROIs, $-.28 < \text{all } rs(13) < .48$, all $ps > .075$.

Within the left caudate, the average between love and relationship duration correlated significantly with the difference in response between beloved-distractor and friend-distractor, $r(13) = -.57$, $p = .028$, which was due to the left caudate response to the beloved-distractor getting smaller as the duration of the love and the relationship increased, $r(13) = -.53$, $p = .041$. Within the left caudate body, none of the correlations between love and relationship duration and the beta values for each contrast were significant, $-.51 < \text{all } rs(13) < .35$, all $ps > .054$, but the left caudate body response to the beloved-distractor did get smaller as the duration of the love and the relationship increased, $r(13) = -.54$, $p = .036$.

Within the left putamen, the average between love and relationship duration correlated significantly with the difference in putamen response between beloved-target and friend-target, $r(13) = .58$, $p = .024$, between beloved-distractor and friend-distractor, $r(13) = -.74$, $p = .002$, between beloved-target and beloved-distractor, $r(13) = .63$, $p = .012$, and between friend-target and friend-distractor, $r(13) = -.71$, $p = .003$. Follow-up correlational analyses showed that the left putamen response to the beloved-distractor decreased with love and relationship duration, $r(13) = -.58$, $p = .025$, while the left putamen response to the friend-distractor increased with love and relationship duration, $r(13) = .74$, $p = .001$.

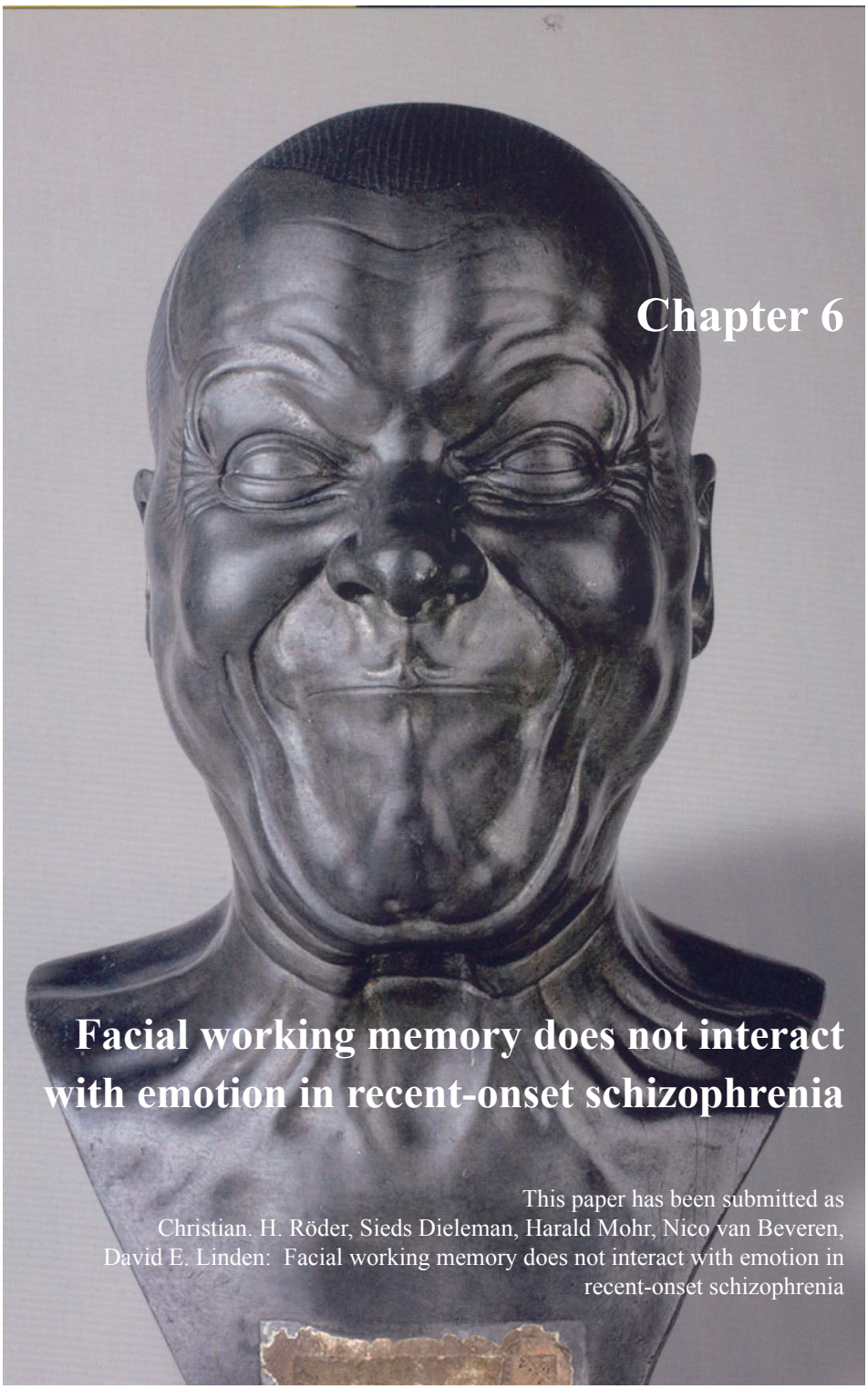
Table s2. Overview of the results of the 2x2 rmANOVAs on the average BOLD signal at 4-6 sec after stimulus onset in the caudate ROIs for each hemisphere separately

ROI	Hemi	Main effect of Love	Main effect of Task	Love x Task interaction
Caudate head	Left	$F(1,14) < 1$, ns	$F(1,14) = 29.6$, $p < .001$*	$F(1,14) = 3.4$, $p = .086$
	Right	$F(1,14) < 1$, ns	$F(1,14) = 16.4$, $p = .001$*	$F(1,14) = 3.3$, $p = .091$
Caudate body	Left	$F(1,14) < 1$, ns	$F(1,14) = 36.5$, $p < .001$*	$F(1,14) = 5.8$, $p = .030$*
	Right	$F(1,14) < 1$, ns	$F(1,14) = 22.2$, $p < .001$*	$F(1,14) = 2.3$, $p = .15$
Caudate tail	Left	$F(1,14) < 1$, ns	$F(1,14) = 12.2$, $p = .004$*	$F(1,14) < 1$, ns
	Right	$F(1,14) < 1$, ns	$F(1,14) = 10.6$, $p = .006$*	$F(1,14) < 1$, ns
Insula	Left	$F(1,14) < 1$, ns	$F(1,14) = 73.1$, $p < .001$*	$F(1,14) < 1$, ns

* = significant

Within the right putamen, the average between love and relationship duration correlated significantly with the difference in putamen response between beloved-distractor and friend-distractor, $r(13) = -.69$, $p = .005$, between beloved-target and beloved-distractor, $r(13) = .54$, $p = .038$, and between friend-target and friend-distractor, $r(13) = -.58$, $p = .023$. Follow-up correlational analyses showed that the right putamen response to the beloved-distractor decreased with love and relationship duration, $r(13) = -.57$, $p = .025$, while the right putamen response to the friend-distractor increased with love and relationship duration, $r(13) = .62$, $p = .015$.

To summarize, the longer the duration of the love and the relationship, the smaller the left caudate and left and right putamen responses to beloved-distractor stimuli and the larger the left and right putamen responses to friend-distractor stimuli.



Chapter 6

Facial working memory does not interact with emotion in recent-onset schizophrenia

This paper has been submitted as
Christian. H. Röder, Sieds Dieleman, Harald Mohr, Nico van Beveren, David E. Linden: Facial working memory does not interact with emotion in recent-onset schizophrenia

Abstract

Deficits in working memory (WM) and processing of information about facial affect are counted amongst the core disturbances of schizophrenia patients (SC). However, the contribution of lower level processing deficits, medication and potential interactions between affective and executive deficits have not been compre-hensively investigated. We addressed all three questions by comparing the perfor-mance of medicated and antipsychotic (AP)-naive SC and healthy controls for WM for face emotion and identity. A facial matching task was used as a control condition.

39 SC and 39 HC matched for sex and age performed a parametric WM-paradigm. Subjects were asked to memorize facial identity or expression. After a delay of 8000 ms subjects decided whether the target matched one of the previous stimuli. In the control condition the same stimuli were presented simultaneously and subjects had to decide whether the target matched one of the other stimuli. Both patient groups performed worse than HC on both versions of WM, but only AP-naïve patients performed worse than HC on face matching. The WM impairment in schizophrenia was not modulated by demands on emotion processing. The cognitive and positive factor derived from PANSS correlated significantly with performance impairments. Impairments in WM-performance are already present in recent-onset SC and AP-naïve patients. Although patients are also impaired in emotion recognition, these impairments do not interact, suggesting different underlying processes for WM and emotion processing. The association of WM impairment with positive symptoms supports the clinical relevance of these findings.

Introduction

Schizophrenia is characterized by both cognitive and emotional disturbances, which substantially influence quality of life and social functioning [1, 2]. Both disturbances are already present at the onset of the disease [3, 4]. One cognitive domain that is strongly impaired in schizophrenia patients (SC) is working memory (WM). Patients are impaired in all major modalities of WM, including verbal [5], spatial [6] and auditory [7] domain WM for context information [8], and for faces [9]. WM deficits are correlated with poor functional outcome [10, 11].

Impaired processing of facial emotion expression is another common deficit [12] and correlates with symptom severity [11, 13]. SC are impaired in recognition [14], matching and labelling of facial expression [9], especially in matching emotions when faces displaying the emotions have different identities [15]. Such deficits are already present in first-episode patients [3] and correlate with symptom severity [11, 13]. According to Bruce and Young [16] face recognition relies on different systems for identity and facial expression. Recent findings call this separation into question [17, 18] because emotional salience supports working memory, suggesting an interaction between identity memory and emotional processes, as has been described for long-term memory [19].

Several studies have investigated WM for faces in SC [9, 15, 18, 20-23]. Most of them used different study designs, which complicates their evaluation and not all [9, 21] used faces with different emotions. When emotions were implicitly modulated [18, 20] faces displaying negative expressions increased performance in SC, but there is some discrepancy as to whether such effects are also present in HC [18] or not [20]. Bediou et al. [15], Martin et al. [23], and Gooding and Tallent [22] explicitly investigated differences in WM for identity or emotional expression of faces. In all three studies SC performed worse in the emotion compared to the identity task. However, only a load of one face was used, which can give rise to a ceiling effect [24]. In addition, Bediou et al. [15] and Martin et al. [23] used delays of one second only, and in the study of Gooding and Tallent [22] the differences between identity and emotional expression task was not supported by statistical interaction analysis.

To examine WM-performance for emotional expression we developed a paradigm in which either identity or emotional expression of faces had to be memorized in a delayed-match-to-sample task. As a control-task participants had to perform a facial matching-task using exactly the same stimuli as in the WM-task. This paradigm was designed to address the question whether patients would show a specific deficit in WM for emotions over and above the well-documented deficits in general WM and emotion recognition. We hypothesized that WM for emotional expression would be specifically impaired in SC because of the interaction of damage to the WM and emotion processing systems. Moreover, we expected impaired emotional WM to correlate with psychopathology, because of theories implicating impaired social cognition in the generation of psychotic symptoms [25]. At last, we examined, whether patients treated with antipsychotics (SC-

med) would perform better than antipsychotic-naive patients (SC-naive). The existing literature is contradictory with respect to the effects of antipsychotics on cognitive function. Single studies [26, 27] found no effects, while meta-analyses reported improvement with first [28] and second-generation antipsychotics [29]. Affect recognition seems to be unaffected by medication [30], with the possible exception of anger [31].

Material and methods

Participants

We studied 39 patients with recent-onset schizophrenia (defined as illness duration < 5 yr) and age between 16 and 35 years (mean age 24.0 years [SD=4,1, range=17-32, 36 male, 3 female]). 17 were medication-naïve (mean age 23.7 years [SD=4.5, range=17-29,] all male) and 22 on a stable dose of medication (clozapine 3, cyclopentixol 1, haloperidol 2, olanzapine 6 quetiapine 2 and risperidone 8) for at least 4 weeks (mean age 24.2 years [SD=3.8, range=18-32,]). Thirty-nine age- and gender-matched healthy volunteers [HC] (mean age 24.6 years [SD=4.1, range=18-31]) were selected as a control group. Groups did not differ in age ($F(2)=0.433$, $p=.65$). All patients were or had been hospitalized in our department and were diagnosed according to DSM-IV criteria. Diagnoses were made by clinical consensus amongst clinicians highly experienced in working with patients with psychosis (C.H. Röder and N. van Beveren) and were confirmed from case-notes using OPCRIT criteria [32]. 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 either as the time of occurrence of positive symptoms or 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 HC met criteria for a current diagnosis or history of any axis I disorder, serious somatic disorder or any cerebral trauma as assessed by questionnaire and personal interview. Because of the frequent methodological problems when trying to match SC with HC on variables such as education or intelligence [33], we decided not to match HC with the two patient groups on level of education.

The study was approved by the local research ethics committee and subjects gave written informed consent before participation.

Dose of medication was calculated in chlorpromazine (CPZ)-equivalents [34, 35]. Current psychopathology was rated with the Positive and Negative Symptom Scale (PANSS) [36] at the day after testing. Extrapyramidal symptoms were scored using the Extrapyramidal Symptom Rating Scale (ESRS) [37].

Emotional working memory task (WM)

A total of 177 faces were taken from two picture libraries [38, 39], displaying angry, disgusted, fearful, happy, sad, surprised and neutral expressions. Stimuli

Table 1 Demographic charactreristics of participants

Characteristics	Healthy controls n=39		Schizophrenia patients n=39		Schizophrenia patients n=22 medicated		Schizophrenia patients n=17 unmedicated	
Gender								
female	3		3		3		0	
male	36		36		19		17	
	mean	range	mean	range	mean	range	mean	range
Age (years) #	24,64	18-31	23,95	17-32	24,18	18-32	23,65	17-32
	mean	SD	mean	SD	mean	SD	mean	SD
Years of education **	11,97	0,16	10.28	1.96	10.14	2.5	10.47	.943
PANNS-Factors§			mean	SD	mean	SD	mean	SD
Positive *			12.7	5.4	10.32	4.87	16.06	4.30
Negative #			15.7	6.9	17.00	6.85	13.88	6.78
Excitement #			8.3	3.1	7.55	2.39	9.31	3.77
Depression #			7.5	2.5	6.95	2.73	8.25	2.02
Cognition #			13.4	4.3	12.45	3.52	14.69	5.04
Medication					CPZ-eqivalents **			
					mean	SD		
Clozapine				13.6%	625.0	241.1		
Cyclopentixol				4.5%	750.0			
Haloperidol				9.1%	150.0	42.4		
Olanzapine				27.3%	141.7	49.2		
Quetiapine				9.1%	800.0	452.5		
Risperidone				36.4%	220.4	42.2		

** $p < .01$ * $p < .05$ # no significant differences # no significant differences

were all aligned to a size of 13.5° horizontally and 11.5° vertically. Hair and clothing were removed to ensure that task performance relied on facial features only. Stimulus presentation was controlled by a personal computer running ERTS (Berisoft GmbH, Germany).

One, two or three faces were presented sequentially for 400 ms each on a 20-inch computer-screen placed 60 cm in front of the subjects. Participants were asked to memorize either emotional expression or identity of the faces, indicated by an instruction preceding every trial. After 8000 ms a test-stimulus appeared and

participants had to make a forced-choice via two keys on a computer-keyboard, whether they had seen the test-stimulus in the present trial. Participants were asked to emphasize accuracy over speed. In case of emotion, faces had the same identity. In case of identity, faces displayed the same emotion. Three blocks of 30 trials had to be performed. Stimulus-order was randomized in each block. Breaks between blocks were according to participants needs. Participants performed a practice trial with stimuli not used in the test condition to get accustomed to the task. Stimuli were balanced for gender, correct and incorrect trials and for emotion and identity, respectively.

Emotional matching task (MT)

Using the same stimuli as in the working memory task we designed a matching task as control task. Stimuli of each trial were presented simultaneously with the test stimulus, so participants had to match the test stimulus with 1, 2 or three faces. Sample stimuli were presented in the upper row and test stimulus in the middle of the lower row. Pictures varied in size from 28.1 ° horizontally and 20.7° vertically (3 faces) to 8 ° horizontally and 20.7° vertically (1 face). Each stimulus was presented for 3000 ms. Participants were asked to decide whether the face in the lower row matched one of the faces in the upper row. Each trial was preceded by an instruction (emotion or identity) for 1000 ms. Participants received the same instruction as in the WM-task and performed a training session.

Statistics

Data were analysed with SPSS 19. A-prime scores were calculated as measure of signal detection sensitivity [40] to detect an interference effect. A-prime increases from 0.5 for chance performance to 1 for perfect performance. A-prime was used instead of d-prime because A-prime is more robust against violations of the assumption that the variances of the hypothetical distributions are equal and does not suffer from the indeterminacy of d-prime that occurs in the absence of false alarms. A-prime values were calculated for each participant following the formula by Grier [40].

Reaction times (RT) were analysed only for correct trials, after RTs with more than 3 standard deviations were excluded from analysis.

Because of low accuracy in patients in the high load condition, a thorough statistical analysis with separate load-conditions was not possible. We collapsed all data from each task in one A'-value for the WM and matching-task each.

Main effects and interactions were further analysed with post-hoc t-tests. Influences of psychopathology and medication were analysed by calculation of Spearman-correlations between A'-values and values of the five factors (negative, excitement, depression, positive, cognition) of the PANSS derived from factor-analysis [41] or chlorpromazine-equivalents, respectively.

All tests were Greenhouse-Geisser corrected and p-values were corrected for multiple comparisons where appropriate. Age and level of education between

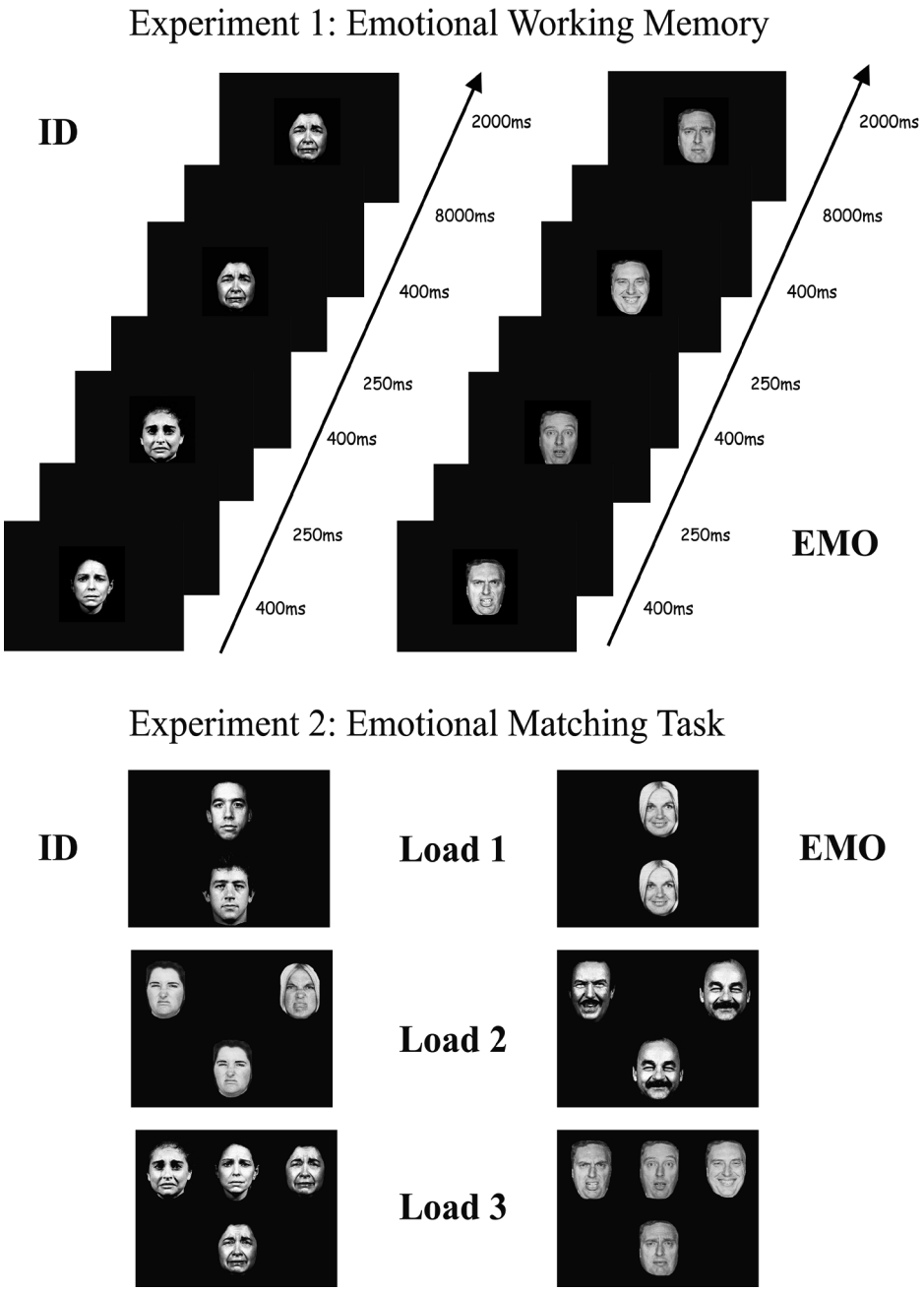


Fig 1. Study design of the WM task depicted for load 3 (left: identity condition; right: emotion condition) in the upper half, stimuli of the Matching Task in the lower half. For detailed information see method section.

groups were tested with one-way ANOVA. Psychopathology ratings between patient-groups were tested with independent t-test. Error probability was set at $p < .05$ (two-tailed).

Results

Groups differed in level of education (HC 11.97 years, SC-med 10.14 years, SC-naive 10.47 years, $F(2, 75)=14.64$, $p<.001$). HC differed significantly from SC-med ($p<.001$) and SC-naive ($p=.002$), but patient-groups did not differ ($p=.76$). These differences may be expected given that schizophrenia is commonly associated with lower educational achievement [42]. SC-naive had significantly higher values for the positive factor ($t(37)=3.77$, $p<.001$) than SC-med, but did not differ on any of the other factors (all $p>.1$). Duration of illness in months was descriptively longer in the medicated group (median: SC-med 19 vs. SC-naive 10, Mann-Whitney-test, $p=.156$).

Accuracy

We performed a mixed repeated-measurement ANOVA with emotion (ID, EMO) and task (WM, MT) as within-subject factors and group (HC, SC-med, SC-naive) as between-subject factor. We found a significant main effect for task ($F(1, 75)=204.5$, $p<.001$, partial-$\eta 2=.73$), group ($F(2, 75)=13.17$, $p<.001$, partial-$\eta 2=.26$), a trend-level significant effect for emotion ($F(1, 75)=3.65$, $p=.06$, partial-$\eta 2=.05$) and significant two-way interactions for task-by-group ($F(2, 75)=9.31$, $p<.001$, partial-$\eta 2=.2$) and emotion-by-group ($F(2, 75)=3.33$, $p=.041$, partial-$\eta 2=.08$). However, we found no significant interaction task x group x emotion ($F(2, 75)=0.803$, $p=.452$), which would have indicated modulation of the WM deficit in schizophrenia by emotion processing.

Post-hoc t-tests revealed that HC performed overall better than SC-naive ($t(54)=4.58$, $p=.001$) and SC-med ($t(59)=3.36$, $p=.001$), and that SC-med were marginally better than SC-naive ($t(37)=1.92$, $p=.063$).

Post-hoc t-tests for the two interactions revealed that HC performed better in the WM-task than SC-med ($t(59)=4.73$, $p<.001$) and SC-naïve ($t(18.5)=4.66$, $p<.001$), and SC-med better than SC-naïve ($t(23.62)=.2134$, $p=.043$). In addition, HC performed trend-level significantly better than SC-naïve in the matching task ($t(18.26)=.2043$, $p=.056$). Similarly, HC performed better than SC-med ($t(25.71)=3.275$, $p=.003$) and SC-naïve ($t(17.06)=3.908$, $p=.001$) when emotional expressions were relevant across both tasks, and. SC-med performed marginally better than SC-naïve ($t(37)=1.948$, $p=.059$). All groups performed better in the matching than the WM-task (HC: $t(38)=7.063$, $p<.001$; SC-med: $t(21)=9.646$, $p<.001$; SC-naïve: $t(16)=7.312$, $p<.001$). SC-naïve furthermore performed nearly significantly worse when the tasks explicitly required processing of emotional expressions. ($t(16)=2.019$, $p=.061$).

HC and SC showed similar effects of load changes in both versions of the WM task with a decrease in accuracy with increasing load ($F(1.442, 1.659)=82.498$,

p<.001, partial-η2=.524) but no interaction between load and group (F(2.885, 108.182)=0.596, p<.612, partial-η2=.016).

Reaction times
HC controls had overall faster reaction times than SC-med (t(59)= 2.74, p=.008) and SC-naive (t(54)= 2.10, p=.041), while patient groups did not differ (t(27)= 0.23, p=.82), ruling out speed/accuracy trade-offs.

Correlations with symptoms and antipsychotic treatment
We calculated correlations between A'-values for the emotion and identity condition of both tasks with the five PANSS-factors. The cognitive component correlated negatively (all r<-.6; p<.001) with the A-prime values for emotional WM and MT-task, and the positive component with the A-prime values for emotional WM (r=-.55, p<.001). No correlations were found between A'-values and other PANSS-factors. In addition no significant correlations were found between A'-values and CPZ-equivalents, even when correlations were calculated for SC-med only.

Discussion

In this study we examined facial WM for identity and emotional expressions. We found that patients have a general WM-impairment for facial stimuli. This was significantly more pronounced in antipsychotic-naïve patients (SC-naïve) than treated patients (SC-med). In addition, SC-naïve performed worse than healthy controls (HC) in the control task, but SC-med performed similarly as HC.
Both SC-med and SC-naïve were significantly impaired compared to HC when emotional expressions either had to be memorized or matched. This deficit was similar in the WM compared to the matching task. Thus we find two general deficits, WM impairment and impairment in processing emotional expressions,

Table 2: Behavioural data of task performance

	Healthy control subjects n=39				Patients with Schizoprenia medicated n=22				Patients with Schizoprenia unmedicated n=17			
	Aprime		RT (ms)		Aprime		RT (ms)		Aprime		RT (ms)	
WM	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
ID	0,88	0,06	952	132	0,82	0,07	1098	181	0,75	0,13	1030	183
EM	0,88	0,05	1010	139	0,79	0,11	1125	187	0,72	0,12	1033	230
MT												
ID	0,93	0,08	1400	219	0,92	0,07	1506	186	0,89	0,14	1575	265
EM	0,95	0,04	1481	221	0,92	0,07	1582	200	0,85	0,15	1617	280

which are independent from each other. The latter finding suggests a deficit in explicit processing of emotional expressions, which has been suggested earlier [18]. However, our study design did not allow to examine implicit effects of specific emotions.
Another important finding of our study is that WM and emotion processing defi-

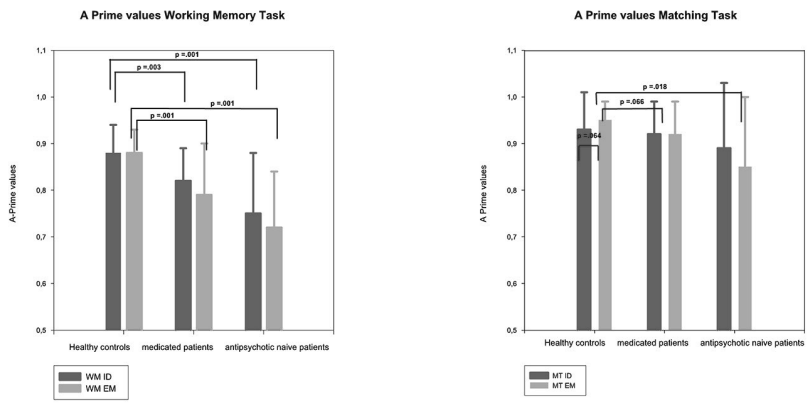


Fig 2. On the left A-prime values of the WM task, on the right A-prime values of the Matching task. Y-bars represent standard deviation.

cits were not merely a consequence of treatment with antipsychotic medication. First at all, both deficits were in fact greater in the medication naive group, and secondly, CPZ-equivalents did not correlate with performance in SC-med. Finally positive symptoms were associated with impaired WM-performance, confirming the functional significance of this cognitive impairment in schizophrenia.
To our knowledge this is the first study investigating working memory for emotional faces in medication-naive patients with recent onset schizophrenia. All previous studies on this topic examined chronic patients [15, 18, 20, 22, 23]. Others used standard WM-paradigms, while inducing emotional states [43, 44].
Both findings are in accordance with previous work [15, 18, 20, 22, 23, 45], in which impaired WM-performance for faces is described. Two studies reported a benefit for angry expressions on WM-performance [18, 20]. In both influence of emotion was examined implicitly. Three studies reported worse performance when emotional expressions compared to identity of faces had to be remembered [15, 22, 23]. The influence of psychopathology on WM performance differed between studies. Martin et al. [23] and Gooding and Tallent [22] found a significant

negative correlation between negative symptoms and WM-performance for both the identity and the emotional expression task, but Bediou et al. [15] and Becerril and Barch [20] found no correlations between WM performance and psychopathology.

Deficits in SC of immediate [15, 26] matching of emotional expressions have been reported. However, patients performed as well as controls in the emotion condition, when both faces had the same identity, but worse when identity differed [15]. While Addington [26] found a small correlation with PANSS-negative values, Bediou et al. [15] found no correlation with psychopathology.

The only study calculating correlations between WM performance and CPZ-equivalents found no correlation [18]. This is in accordance with several studies, which have demonstrated that medication does not improve cognitive functions [26, 27] or affect recognition [30] in SC over time, but contradictory results have also been found [28, 46, 47]. In our study antipsychotic-naïve patients showed impairments in WM-performance and processing of emotional expressions, compared to treated patients. However, this was not accompanied by significant correlations with CPZ-equivalents, as it has been found earlier [28]. In addition, patient groups differed with regard to psychopathology only for positive psychopathology, suggesting that psychotic symptoms may have a stronger impact on WM performance and processing of emotional expressions than treatment by itself. The highly negative significant correlations between the cognitive factor and performance in the emotional versions of both tasks suggest a strong impact of cognition on processing emotional expressions, with an even detrimental effect of psychotic symptoms. Previously, correlations between changes in positive symptoms and performance on a spatial WM tasks have been reported [47]. Although these results were obtained in the same patient group before and after treatment, it seems reasonable to assume that our findings rely on the same mechanism of reduced positive symptoms in SC-med. In addition, it has been found that higher psychopathology ratings do not affect cognitive and emotional functions in general, but seems to have some specificity for recognition of facial effect [48]. This is in line with our results, which show no differences in accuracy between the two patient-groups in the MT-task, but impairments in working memory performance independent from the modality, and greater impairment in SC-naive when emotional expressions have to be processed.

In contrast to the suggestion that cognitive impairments mainly correlate with negative symptoms [13], we found no correlations between negative symptoms and accuracy. Disorganization or negative symptoms may be correlated with different cognitive profiles of impairment [49].

The literature on structural and functional neuroimaging provides potential clues as to the neural systems responsible for the impairments in WM in schizophrenia. Volumetric MRI measurement has indicated a reduction of the fusiform gyrus in patients with schizophrenia [50], which might explain general deficits in face processing in patients with schizophrenia, but these findings were obtained in

chronic patients. Extrastriate visual areas have also been implicated by activation changes on fMRI during extraction of facial emotion [51] and during face WM [45, 52] in SC. However, directions of effects vary (hyper- vs. hypoactivation in the patients), and the same is the case for the prefrontal activation patterns [20, 21, 45, 52]. It has been shown earlier [53], that cognitive demands, for example rating of valence, may decrease brain activity in limbic regions and increase that in frontal and parietal regions. It seems therefore reasonable that the underlying pathophysiology for the observed results is to a certain extent based on impairments of perceptive and executive functions. Contradictory results from imaging studies [54, 55] leave some uncertainty about the involvement of the limbic system during both tasks. The imaging literature thus indicates a potential involvement of alterations in higher visual, prefrontal and limbic [21, 56] processes in the WM impairment in SC, but does not at present allow for the construction of a unitary model.

There are some limitations to our study. We cannot definitely rule out contributions from perceptual and visual encoding deficits in SC [57]. However, the results of the matching task demonstrate no differences between performance in HC and SC-med, suggesting that the observed WM impairment is not based on perceptual deficits. Medicated patients received a manifold of antipsychotics, but groups were to small to compare possible differences between the individual antipsychotics. Healthy controls and patients were not matched for level of education. However, differences in WM performance between the two patient groups, which did not differ in level of education, suggest, that also factors specific to schizophrenia may explain the results of our study.

In conclusion, impaired face WM and processing of emotional expressions are already present in recent onset schizophrenia, and not a consequence of chronicity or medication. The impairment is more pronounced in antipsychotic-naive patients, but this can be an effect of the higher level of psychotic symptoms.

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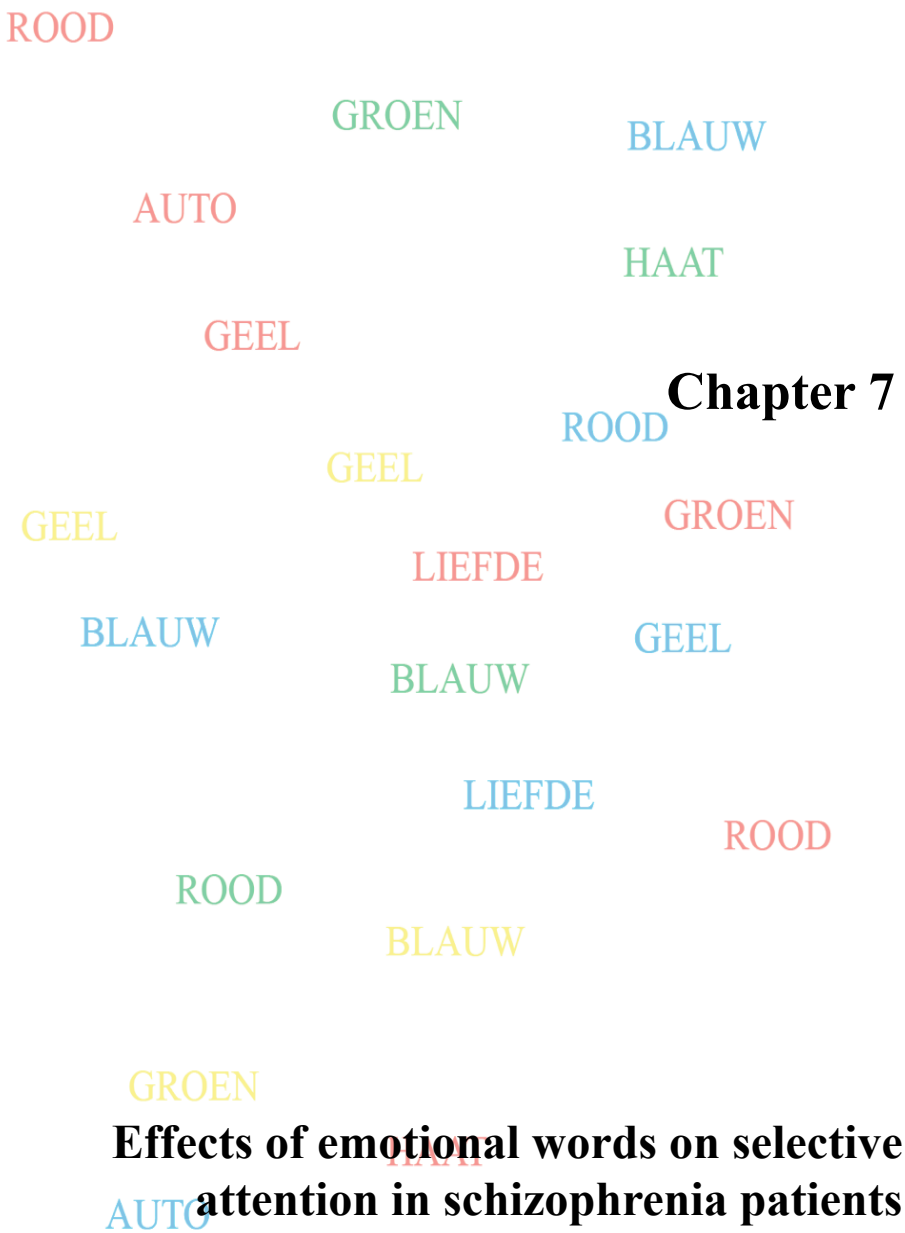

Chapter 7

Effects of emotional words on selective attention in schizophrenia patients

This paper has been submitted as
Christian. H. Röder, Sieds Dieleman, A.Sterrenburg, Nico van Beveren, Frederik M. van der Veen: Effects of emotional words on selective attention in schizophrenia patients

Abstract

In patients with schizophrenia an impairment of selective attention has been repeatedly described. 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 viewed word with negative, neutral and positive words. All word categories were presented intermixed in a pseudorandomized order. Patients had as expected longer reaction times (RT) to all stimuli. As a main result, 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 the emotional categories only were analysed. Although recent-onset patiens show a reduced speed of processing, their ability to process implicit emotional properties of verbal stimuli in a task examining selective attention is unaffected.

Introduction

In patients with schizophrenia impairments in emotional processing are not only found in the recognition of emotional expressions, but also seem to affect core cognitive functions such as memory [1, 2] and attention [3]. The influence of emotion on attention has been widely examined in anxiety disorders and depression using an emotional Stroop-task [4], and it has been shown, that word content relevant to one of the disorders increase reaction times.

Two studies using an adapted card-version of the emotional Stroop-task examined patients with persecutory delusions [5, 6]. Patients either suffered from schizophrenia or delusional disorder and were compared to a group of healthy controls and a group of depressed patients. Bentall & Kaney [5] used one condition with words with potentially threat-related content and a condition with words with depressive content. Kinderman [6] used personally descriptive adjectives with negative or positive content. The latter reported higher 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. In contrast, Bentall & Kaney [5] reported a significantly higher effect of interference for deluded patients for threat related words compared to both control groups.

An fMRI-study [7] with an adapted Stroop-task, using pictures combined with congruent and incongruent emotional words found no differences in reaction time (RT) between schizophrenic patients and healthy controls for both congruent and incongruent trials. Besides the correct response rate obtained by dividing individual number of correct responses by the total number of responses, task performance efficiency was calculated. Here the correct response rate was divided by the individual mean reaction time of correct responses. For correct response rate groups differed significantly, but no interaction between group and congruency was found. However, patients had significantly lower task performance efficiency in the incongruent condition than healthy controls. On fMRI-level a different pattern of BOLD-signal changes were found in the subgenual anterior cingulate gyrus, a reduction during incongruent trials in healthy controls, but not in the patient group.

Two recent studies examined a verbal emotional Stroop-test in chronic schizophrenic patients [8, 9]. Phillips et al. [9] found no differences between patients and healthy controls, not even in absolute reaction times. Negative words caused interference and positive facilitation. However, patients with high amounts of disorganization revealed stronger interference for words with negative and stronger facilitation for words with positive content compared to patients with low amounts of disorganization. In contrast, Demily et al. [8] found that in both patients and healthy controls positive and negative words caused interference, without a significant group by word interaction, but overall patients had increased reaction times.

To our knowledge ours is the first study that used an emotional Stroop-task in recent-onset schizophrenic patients to examine the effect of emotion on selective attention. In contrast to Demily [8] and Phillips [9] we examined patients with short illness-duration with 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 with recent-onset schizophrenia (defined as duration of illness < 5 yr, 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 [10]. 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) [11] 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). Both groups did not differ in psychopathology ratings and age. Because the group of unmedicated 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. 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 [12], 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.

Emotional Stroop-task

Participants were examined with a modified Stroop-task, previously used in an FMRI study with healthy controls [13]. A word was presented every 2 s against a black background and stayed on the screen until a response was given. In to-

Table 1 Demographic charactreristics of participants

	Healthy controls n=26		Schizophrenia patients n=30	
	mean	range	mean	range
Age (years) #	23.9	18 - 32	23.95	17 - 32
	mean	SD	mean	SD
Years of education **	11,96	0,2	10.43	0.78
Illness duration (months)			18	13.5
PANNS-Score			mean	SD
Positive			11.7	7.2
Negative			15.4	8.7
General			26.4	13.1
Total			53.6	26.9
Medication	CPZ-eqivalents **	n	mean	SD
Clozapine		7	423	108
Cyclopentixol		2	275	35
Haloperidol		7	263	70
Olanzapine		2	175	107
Quetiapine		2	640	
Risperidone		1	300	
Medicated patients (total)		21		
free		9		

** $p < .01$ # no significant differences

tal 152 words (Font: Helvetica, letter-size 48) were presented in a pseudorandomized 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-test we used four colour words: blauw (blue), groen (green), rood (red) and geel (yellow) and 72 non-colour words. 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 trial 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 analyzed 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 analyzed with repeated-measurement ANOVA and t-tests where appropriate using SPSS 20. Influence of psychopathology or medication expressed in CPZ-equivalents were analyzed 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. 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 ($F(3.2,173,9) = 2.079$, $p<.1$, partial-$\eta 2 = .037$). Thus overall patients had longer RT, but effects of word-type were the same between groups.

Because we were mainly interested in the differences between the three emotional word categories we performed planned contrast between negative and neutral

words and positive and neutral words respectively. These showed a significant longer RT for negative words 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. Both, facilitation (T(55)=2.066, p=.044) and interference (T(55)=7.789, p<.001) where significant, but when corrected for multiple comparisons (p=.05/2 =.025) only interference remained significant.

Table 2 Mean reaction times RT in ms and mean errors (absolute numbers)

	Congruent	Incongruent	Neutral	Negative	Positive
RT					
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)	.06 (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)

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 Therefor, 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. Again, we found a main effect for group ($F(1,54) =15.180$, $p<.001$, partial-$\eta 2 =.22$) and word-type ($F(1.9, 104.3) =3.832$, $p =.026$, partial-$\eta 2 =.07$), but no significant interaction ($F(1.9, 104.3) =0.830$, $p =.435$, partial-$\eta 2 =.063$). 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 $p >.17$).

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-$\eta 2=.32$), but no significant main effect for group or group by word-type in-

teraction.
Our main interest were the effects of emotional word category on error rate, thus we performed plan contrast between negative and neutral as well as positive and neutral words. Due to the low error-rate non parametric test were used. We found significantly higher error rates for positive words in patients (HC: 0.37; SC: 1, Mann-Whitney-U: p=.018).
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. Both, congruent ($T(55)=2.935$, $p=.005$) and incongruent ($T(55)=6.714$, $p<.001$) colour words had higher error rates than non-colour-words.
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 remained all non-significant (all $p > .13$).

Discussion

To our knowledge this is the first study, that used an emotional Stroop-task in recent-onset schizophrenic patients. 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 neutral words, however no group differences or interactions where found. So, 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. So, schizophrenic patients are distracted in the same way by the content of negative words and not affected by positive words as healthy controls. A slightly different result was found for errors. While for the standard Stroop-task both groups had similar error rates, patients had significantly more errors in positive words, while error rates for neutral and negative words were similar between groups.
Previous studies reported that schizophrenic patients and healthy controls had the same amount of interference by incongruent colour words compared to neutral words and even an increased facilitation by congruent colour words [14-17]. However, a recent meta-analysis reported increased interference in schizophrenic patients [18]. But as Westerhausen et al. [18] and Henik & Salo [17] 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, some reported increased facilitation in

schizophrenic patients compared to healthy controls [16, 19] others found no differences [20]. However, most studies are performed in chronic patients. Our results, no differences in facilitation between patients and controls, are in accordance with the results of Chen et al. [21] , who examined a Stroop-task in a sample of first-episode schizophrenic patients, which most strongly resembles our sample of recent-onset patients, except that there mean age was 10 years higher than in our sample. Remarkably, the subgroup of treated patients showed a facilitation effect, which disappeared during retesting after 4 month [21]. We did not find any differences between treated and untreated patients, but for this comparison our study probably was underpowered.

Five studies used emotional Stroop tasks in schizophrenic patients [8, 9, 22] or deluded patients [5, 6]. Studies differed in some aspects from ours. Bentall&Kayne [5] and Kinderman [6] used card-versions of the Stroop-task. Park et al. [22] used an adapted versions with emotional word-picture (in)congruency. Demily et al. [8] and Phillips et al. [9] 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 [5, 6] found increased interference for negative words in patients compared to healthy controls, and Kinderman [6] also for positive words. Park et al. [22] found no group differences in interference regarding RT, but for performance efficiency patients had greater interference in the incongruent emotional word-picture condition. The studies most similar to ours [8, 9] 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. [8] report an interference effect, while Phillips et al. [9] found no effect, similar to the observation in our sample. Importantly, our findings that all effects (cognitive and emotional Stroop-test) did no differ significantly between patients and controls, are in accordance with the results of both studies.

Williams et al. [4] 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 [5] and in healthy controls [23]. However, in these studies negative or threatening words were used. Neither in previous studies [8, 9] 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 [17, 18]. However, all studies reported an interference effect for negative words, suggesting different impact in 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 schizophrenic patients [15, 16, 19], 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. [8]. 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 [24, 25]. As Compton et al. [24] 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. Another study [25] found differences in BOLD-signal comparing a cognitive with an emotional counting Stroop task. Both studies used a blocked design and found a habituation of BOLD-signal differences during the task and in addition 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 they recruit additional resources in the prefrontal lobe. In addition, impaired performance is associated with reduced BOLD-signal in the prefrontal cortex [26, 27]. These results have to be viewed with some caution, firstly because an adapted Stroop task was used and secondly not reaction times 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 due to the typically observed reduced speed of processing [28].

There a some limitations to our study. Our samples were not matched with respect to level of education. However, in spite of significant differences between schizophrenic patients and healthy controls, Stroop effects did not differ between groups, so we would like to suggest that these differences are not relevant for the interpretation of our data. Emotional words were not evaluated for its emotional impact (valence and arousal) by the participants of the study. 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. [8].

In conclusion we find a general slowing in RT in recent-onset schizophrenic patients during an emotional Stroop-task, but interference and facilitation did not differ 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 schizophrenic patients is in-

fluenced by incongruency of colourwords and emotional content of words in the same way as it is in healthy controls.

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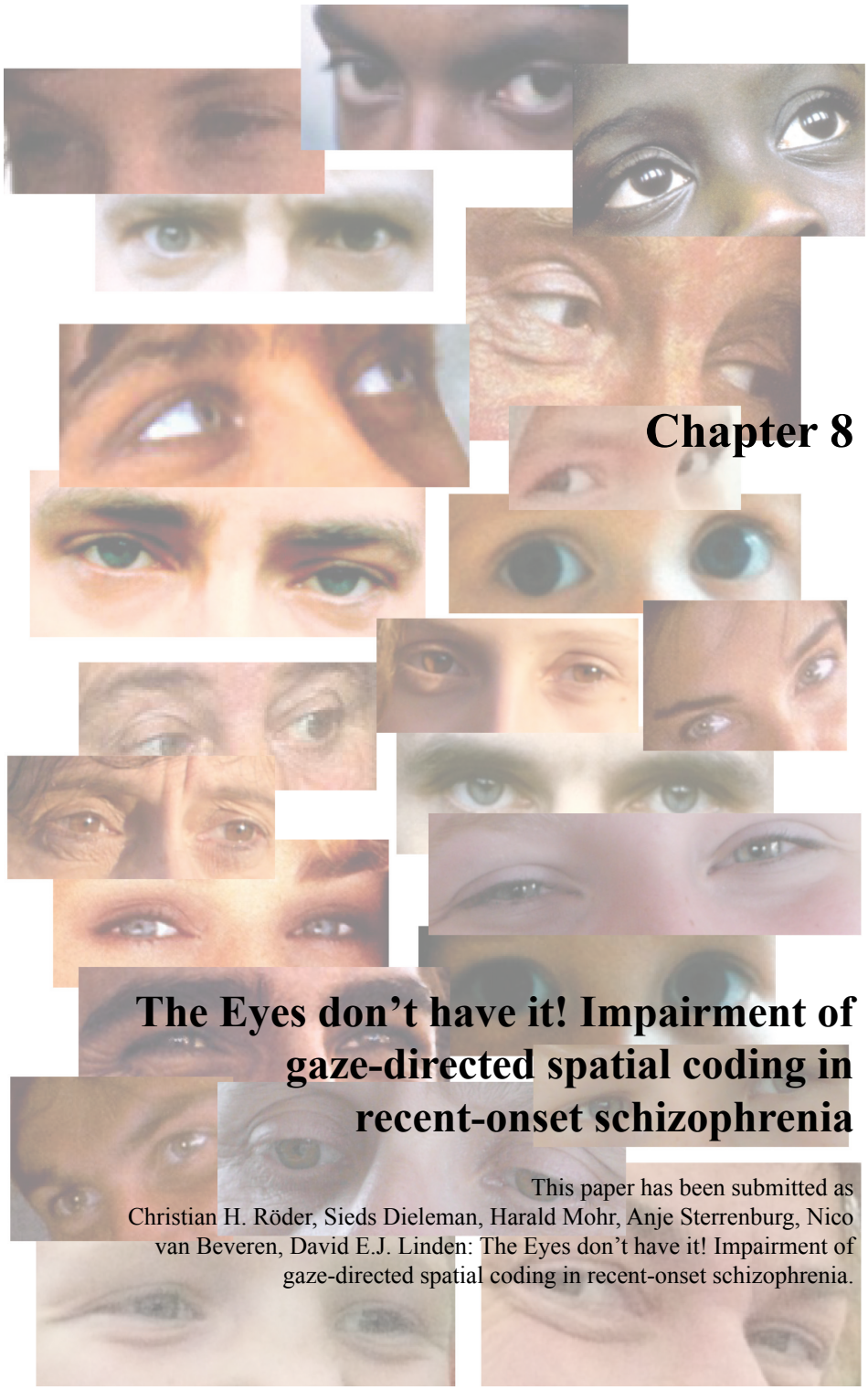

Chapter 8

The Eyes don't have it! Impairment of gaze-directed spatial coding in recent-onset schizophrenia

This paper has been submitted as
Christian H. Röder, Sieds Dieleman, Harald Mohr, Anje Sterrenburg, Nico van Beveren, David E.J. Linden: The Eyes don't have it! Impairment of gaze-directed spatial coding in recent-onset schizophrenia.

Abstract

Patients with schizophrenia (SC) show deficits in the processing of social cues. Little is known whether this deficit in social cognition also influences non-social, "cold", cognition. Interactions between these domains can be tested with a Simon task using social stimuli (gaze direction). We investigated whether the Simon effect, the slowing of reaction times produced by stimulus incongruities in the spatial domain, differs in schizophrenic patients and healthy controls (HC) as a function of the social nature of the cues. Thirty-five recent-onset, male SC and 30 male HC participated in the study. We used the gaze-direction Simon effect paradigm described by Zorzi et al.[1], in which the Simon effect is generated by a schematic drawing of human eyes (social cues) or rectangles (non-social cues). Overall SC had longer reaction times. Furthermore, groups showed a Simon effect in both tasks. While in HC the Simon effect was stronger in the eye-like compared to the rectangle condition, for SC the Simon effect was less strong in the eye-like compared to the rectangle condition. Current psychopathology or treatment with antipsychotics did not influence results. Although the Simon effect is present in SC, the influence of social cues was much reduced in the patient group. The present study supports earlier findings of altered processing of social cues in SC. Crucially; we demonstrated that this deficit in social cueing affects early attentional processes in schizophrenia.

Introduction

Schizophrenia is a psychiatric illness accompanied by both cognitive and emotional disturbances. Cognitive impairments have been found not only in core functions such as selective attention [2], perception [3], speed of processing [4], and working memory [5] but also in social cognition which comprise emotional processing, social perception, attributional bias and theory of mind [6]. In healthy subjects Ziv et al. [7] identified two independent factors for core cognition and social cognition. Deficits in social cognition cannot be entirely attributed to deficits in executive functioning [7]. Similarly, social cognition deficits in schizophrenic patients cannot solely been explained by deficits in core cognitive functions [7, 8]. A meta-analysis found only small to moderate correlations between domains of social cognition and the domains of the MATRICS [9]. Whether altered social cognition influences non-social ("cold") cognition in schizophrenia is largely unknown [10].

We studied this question with a modified version of the Simon task, utilizing gaze-cueing [1]. Gaze-cueing describes the observation that one's attention is directed by the gaze of another person or pictorial stimuli resembling eyes [11]. Gaze-cueing is already present in three month old infants [12]. Multiple studies (see Tipper [13]) have shown that gaze-cueing effects are 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 [14] (congruency-effect). The fact that this effect is fast (within 200 ms of gaze shift) has been interpreted as reflecting an automatic, reflexive and stimulus-driven orienting of attention mechanism.

Gaze is the quintessential social cue [15], and gaze-cues can be effective in guiding or disrupting attention [13], but only few studies have studied this process in schizophrenic patients [16, 17] although impairments in gaze-processing may be relevant for patients' deficits in social interaction [6]. Several studies have examined the perception of gaze-deviation [18, 19] in schizophrenic patients, who recognize correctly that gaze is directed to the left or right [18], but have the tendency to interpret slightly averted gaze as directed to them [19].

Effects of gaze-shift have been further examined in schizophrenic patients using the inhibition of return (IOR)-paradigm [20, 21]. IOR describes the observation, that a cue spatially corresponding to a subsequent stimulus facilitates reaction time to the target stimulus if the interval between cue and stimulus is relatively short (<300 ms), but has an opposite effect with increasing time intervals. IOR has been characterized as a mechanism supporting orientation of attention to novel objects in the environment [22]. Schizophrenic patients performed in an IOR-paradigm as healthy controls [21] when geometrical stimuli were used. When gaze was used in order to direct attention, healthy controls still demonstrated IOR, but schizophrenic patients had shorter reaction times to stimuli in the cued hemifield even after a time-interval of 2000 ms [21]. However, others found impairments of IOR in patients also for geometrical stimuli [20].

In all these studies, a non-informative lateralized cue precedes a target-stimulus. In contrast, the Simon-task requires a response to a lateralized stimulus, but the stimulus' spatial property is task irrelevant [23]. It is assumed that an automatic response-activation to the irrelevant stimulus-feature (spatial location) interferes with task-instruction to react on the task-relevant feature [24].
In the standard procedure for eliciting the Simon-effect participants respond with the left or right hand to a non-spatial stimulus-dimension (color or shape) with stimuli being presented on the left or right side of the screen [25, 26]. The Simon-effect describes the observation that faster and less error-prone responses are obtained when the task-irrelevant stimulus-location and response are on the same side rather than on opposite sides (congruency-effect).
Zorzi et al. [1] introduced a combination of gaze-directed attention and the Simon-effect. Here two identical stimuli are presented one in each hemifield. Two types of stimuli are used, a colored square surrounded by a rectangle and a colored circle surrounded by an ellipse, the latter resembling eyes. Participants have to react to the stimulus color 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, the in the middle or near either side of the outer shape (rectangle or ellipse)) (see figure 1). They described a "gaze directed Simon effect" [1], caused by the spatial coding of gaze shift, but only with eye-like stimuli, confirming earlier findings examing spatial attention [27].
Akiyama et al. [16] used an adapted version of this task [1] in a group of chronic schizophrenic patients. Gaze-cue stimuli in and black and white or arrows pointing to the left or right were used as cues for subsequently presented target stimuli presented in the left or right hemifield. Thus, Akiyama et al. [16] did not examine the Simon effect but spatial attention. Healthy controls demonstrated significant congruency effects for all three conditions. In contrast, patients had showed a significant congruency effect only for arrows and at trend level for the eye-like stimuli.
The design of Zorzi et al. [1] allows to examine whether the Simon effect is caused by an increase of reaction time (RT) for incongruent stimuli (interference) or a decrease of RT compared to neutral stimuli (facilitation). We aimed to investigate the extent to which social cues influence exogenous attention in patients with recent-onset schizophrenia (SC). We used the same design as Zorzi et al. [1] to examine whether SC 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 HC. We hypothesized that patients would show a smaller Simon effect with the social (gaze) cues.

Methods

Participants

We compared a group of 33 male recent-onset (defined as duration of illness < 5 yr) SC (mean age = 23.5 years, range: 18-34 years) with a group of 30 male HC

subjects (mean age = 24.4 years, range: 18-31 years) matched for age (t=0.753, df=64, p=.454). All participants were right-handed as evaluated with the Edinburgh Handedness Inventory. Mean duration of illness was 22.85 months (range 1 to 58 months, median: 20 month). 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 and diagnosed according to DSM-IV criteria. Diagnoses were made by clinical consensus amongst clinicians highly experienced in working with patients with psychosis and confirmed using OPCRIT criteria [28]. 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. None of the HC 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. HC with a first-degree relative with a history of psychosis or any other serious psychiatric disorder were excluded. All participants were informed over the study by written information and gave informed consent.

Because of the frequent methodological problems when trying to match SC with HC on variables such as education or intelligence [29], 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. Patients had significantly fewer years of education (10.5 vs. 11.9 years, $t(61)=9.336$, $p<.001$).

Actual psychopathology was rated with the Positive and Negative Symptom Scale [30] (PANNS) at the day after testing. Extrapyramidal symptoms were scored using the Extrapyramidal Symptom Rating Scale [31] (ESRS). Ten of the patients were free of medication (3 naïve), all others were on a stable dose of medication for at least 4 weeks. Prescribed antipsychotics were clozapine (7), cyclopentixol (2), haloperidol (6), olanzapine (4) quetiapine (1) and risperidone (3). Dose of medication was calculated in chlorpromazine (CPZ) equivalents.

Mean values for the four PANSS-factors were: positive: 11.6 (SD 6.9); negative: 17.7 (SD 8.2); general: 27.6 (SD 12.3) and total PANSS score: 54 (SD 25). Medicated patients had a significantly longer illness-duration (27 vs. 13 month ($t(27.5)=2.7$, $p=.012$)) and higher total PANSS scores (67.1 vs. 49.5, ($t(31)=2.4$, $p=.025$)). This effect was driven by significantly higher positive scores (16.6 vs. 9.6 ($t(22.7)=3.3$, $p=.003$)). Mean dosage of antipsychotics was 315 (SD 139) CPZ-equivalents.

Materials and Procedure

We used an adapted version of the Simon task [1] (see figure 1). A series of stimuli (either in blue or green) were presented to subjects, either with neutral gaze

Table 1 Demographic charactreristics of participants

	Healthy controls n=30		Schizophrenia patients n=33	
	mean	range	mean	range
Age (years) #	24.4	18 - 34	23.7	18 - 33
	mean	SD	mean	SD
Years of education **	11.9	0.3	10.4	0.79
Illness duration (months)			22	15.8
PANNS-Score			mean	SD
Positive			11.6	6.9
Negative			15.7	8.2
General			26.7	12.3
Total			53.9	25
Medication	CPZ-eqiva-lents **	n	mean	SD
Clozapine		7	423	108
Cyclopentixol		2	275	35
Haloperidol		6	277	65
Olanzapine		4	150	70
Quetiapine		1	640.0	
Risperidone		3	275	43
Medicated patients (total)		23	315	139
free		10		

** $p < .01$ # no significant differences

or gaze to the left or right. Participants were instructed to react to the color 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 color-response hand allocation was balanced over subjects for the two colors. 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 types of stimuli. In the first condition, subjects saw a fixation cross (0.7°x0.7° visual angle) in the middle of the screen, with a square with

a size of 2° surrounded by a rectangle of 8.6° at both sides of the fixation cross. Overall size of the stimulus was 20°.
Squares were always kept in position, but rectangles could be displayed in three different positions. The neutral position left the square in the center 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. Each trial ended with an intertrial interval of 1000 ms. In total 180 trials had to be performed, 90 with green rectangles and 90 with blue rectangles. For each position (neutral, left, right) of the square within the rectangle 60 trials were presented. Prior to testing subjects performed 20 practice 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 in size. In earlier studies normal subjects [1] perceived these stimuli 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 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 and number of errors were recorded. Only reaction times of correct answers were entered into further analysis. Mean reaction times for each condition (neutral, corresponding, non- corresponding) in both tasks (rectangles, eyes) for each subject were calculated. Reaction times of each subjects 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-Smirnow-test on all raw data. Primarily we analyzed the mean values for the three gaze directions in both conditions and groups with a mixed-design ANOVA. In several patient groups higher intra-individual variability has been described [32, 33], 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 [34]. Both were compared with t-test between the two groups. Subsequently we calculated the individual differences between the congruent and incongruent conditions to examine the Simon effect between groups and tasks. At last we are interested in the facilitating and interference effect of spatial coding and therefore calculated both the difference between neutral and congruent and incongruent and neutral trials of each subject for the rectangle and the eye-condition separately. All analyses

were performed by mixed-design ANOVA with the factor group (SC vs HC) as between-subject-factor and condition (rectangle vs. eye) and congruency (congruent, neutral, incongruent) as within-subject-factors. Significant interactions were further analyzed 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 covariances. Error probability was predefined at $p<.05$ (two-tailed) and significance level was adjusted for multiple comparisons where appropriate.

Results

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, schizophrenic patients had significantly longer reaction times (RT) than healthy controls in each subtask with all p-values <.05. (see table 1 and figure 2)

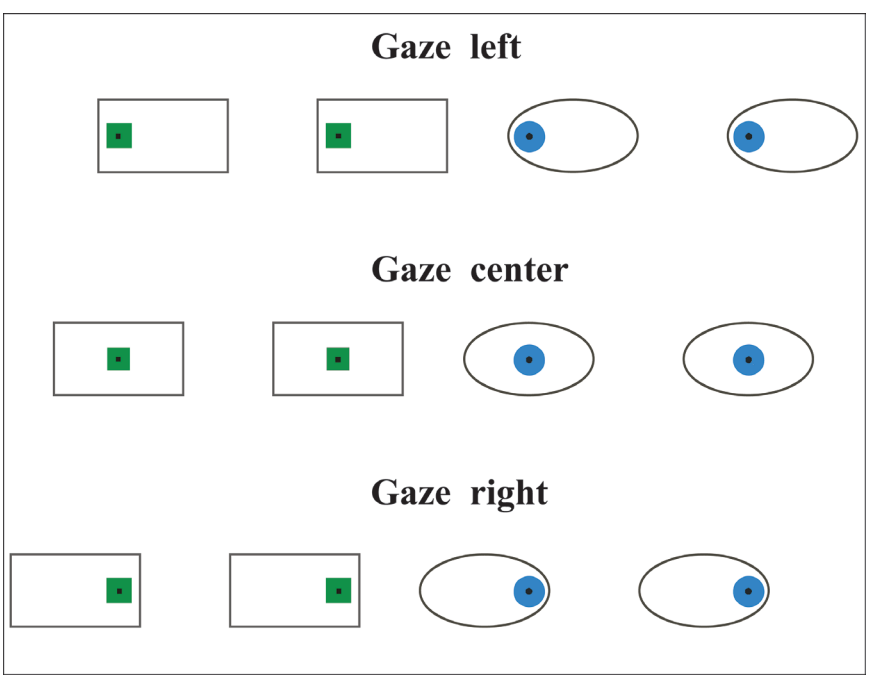

Fig 1. Left rectangle stimuli, right eye-like stimuli. Each stimulus was presented 60 times in random order. During the first run only rectangle stimuli were presented, during the second only eye-like stimuli. Stimuli were either in blue or green in both conditions. Subjects were instructed to push a designated button for each color as fast as possible after stimuli had appeared on the computerscreen

Firstly we performed a mixed design ANOVA on the mean reaction times with gaze direction (congruent, neutral, incongruent) and task (rectangle, eyes) as within subject factor and Group (HC, SC) as between subject factor. The factors gaze direction ($F(1.743;106.316)=5.799$, $p=.006$, $\eta p2=.087$) and group ($F(1,61)=16.479$, $p< 001$, $\eta p2=.216$) had significant main effects. All other main effects and interactions were non-significant. The comparison of the overall intra-individual RT and intra-individual standard deviation between the two groups was 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; $t(55.78)=4.11$, $p<.001$).

We then calculated the Simon effect for both tasks (Congruent - Incongruent) for each subject. These values were entered into a mixed design ANOVA with Stimulus (rectangles, eyes) as with within subject factor and Group (HC, SC) as between subject factor. None of the main effects were significant, but the interaction was significant ($F(1,61)=5.474$, $p=.023$, $\eta p2=.082$). 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, Kolgomorov-Smirnow, $p=.008$), and patients were descriptively more distracted by rectangles (mean difference 19 ms) than by eyes (Mean difference 10 ms, 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 ($p=.05/4=.0125$).

According to Aisenberg and Henik [25] the Simon effect can also be subdivided in interference and facilitating effects. We therefore calculated these values by subtracting the RT for the averted gaze conditions from the neutral position in both tasks (neutral - congruent: facilitation; incongruent - neutral: interference). The mixed design ANOVA with the factors gaze direction (neutral - congruent, incongruent-neutral), stimulus property (rectangle, eye) and group (SC, HC) revealed only a significant 2-way-interaction between group and task ($F(1,61)=5.474$, $p=.023$, $\eta p2=.082$), replicating the results of the ANOVA for the Simon effect. No other main effect or interaction reached statistical significance.

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.

In conclusion, schizophrenic patients had longer reaction times in all conditions, as expected. Furthermore groups showed a Simon effect in both tasks. While the effect for the patient group was descriptively larger in the rectangle condition

compared to the eyelike-condition, the group of control subjects showed the opposite, a significantly larger Simon effect in the eye-like condition compared to the rectangle condition. In addition, the Simon effect in the eye-like condition was significantly greater in healthy controls. 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 schizophrenic patients compared to healthy controls.

First of all, our first hypothesis could be partially confirmed since schizophrenic patients revealed a significantly smaller Simon effect in the eye-like condition

Table 2: Reaction times in milliseconds for healthy controls vs. schizophrenic patients.
Below Simon effect (incongruent condition minus congruent condition)

	Healthy controls n=30		Schizophrenia patients n=33	
	RT (ms)		RT	
Square	mean	SD	mean	SD
Neutral[a]	442	68	542	127
Congruent[b]	442	70	539	136
Incongruent[b]	450	70	558	148
Facilitation	0	26	3	95
Interference	8	21	16	52
Eye				
Neutral[a]	445	65	541	123
Congruent[b]	433	70	540	122
Incongruent[a]	463	74	550	138
Facilitation	12	95	1	43
Interference	18	101	9	52
Simon effect				
Square[c]	8**[#]	24	19	46
Eye[d]	30[#]	30	10**	55

Independent sample t-test: a: p<.001, b: p<.005

Kolmogorov-Smirnow-test: c: Comparison square vs eye in HC p=.008
d: Comparison eye-condition HC vs. SC p=.003

than healthy controls. Patients had nearly no facilitation and a less interference than healthy controls, and thus it seems that patients with recent-onset schizophrenia are less distractible by gaze cueing. These findings are not influenced by psychopathology or dosage of antipsychotics as no correlations were found between PANSS-scales, CPZ-equivalents and RT or the Simon effect. Differences in the response-pattern and reaction times between treated and untreated patients did not reach significance.

The results are in accordance with earlier results [35], which demonstrated a reduced Simon effect for patients with schizophrenia. However, group size in this

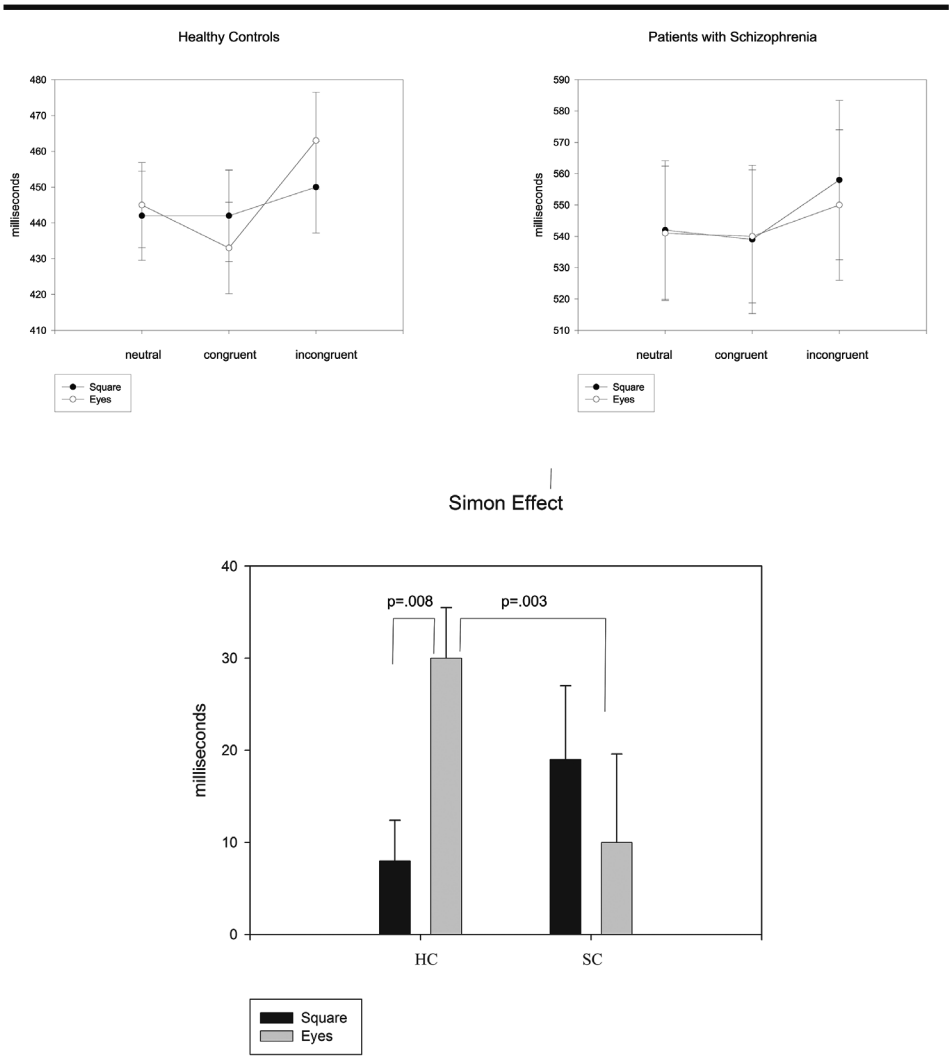

Fig 2. Reaction times for each group separately for both tasks (upper 2 rows). Range of y-axis varies between graphs. Below Simon effect for all groups (left rectangle condition, right eye-like condition)

study [35] was relatively small and patients with predominantly negative symptoms were included, and the effect was only present in the left, but not in the right hemifield. In our study, the reduced Simon effect in the eye-like condition refers more to a stimulus specific impairment in schizophrenic patients than a general deficit in the Simon task for schizophrenia patients. However it has to be taken into account that the design of this study differed from a typical Simon task in that stimuli were presented bilaterally (see figure 1).

Secondly, we reproduced earlier results [1] in healthy subjects. Although a small, non- significant Simon effect could be detected in healthy controls for the rectangle condition, this effect was much bigger in the eye-like condition. However, for the raw RT we could not find an interaction between the two conditions (eye, square) and group. This is probably caused by the much higher intraindividual variability in patients, as shown by a significant higher standard deviation and coefficient of variance.

Recently, a version of the Simon task with a neutral conditions has been developed [25]. In both types of neutral condition an interference effect was present, and in one condition also a facilitation effect was found. Thus interference seems to be a stronger effect than facilitation, which seems to depend on the neutral stimulus. In our study no significant facilitation or interference were detected.

Using the same stimuli as in our study to direct attention to a stimulus appearing in one of the hemifields [16] healthy control subjects had a congruency effect evoked by eyes, rectangles and arrows, directing attention to the hemifield in which subsequently stimuli appeared. In contrast to our results, schizophrenic patients had a nearly significant congruency effect for eyes, but no congruency effect for rectangles. However there are important differences between patient groups of Akiyama et al. [16] and our study. Akiyama et al. [16] examined chronic patients who had more symptoms (total PANSS 82) and used higher doses of medication (12.8 haloperidol-mg equivalents corresponding to 768 CPZ-equivalents). Furthermore the study design differed from ours in several aspects. Firstly, in the task of Akyama et al. [16] gaze deviation preceded appearance of stimulus, on which subjects had to react, while in our task gaze was an inherent, but irrelevant stimulus property.

Secondly, while stimuli itself had a spatial property by being displayed either in the left or right hemifield and response had to be performed only by one hand and key [16], in our task the specific aspect was the lateralized motor response. Thus differences in task concept and patient population may account for the differences between our and Akiyama et al.'s [16] results.

In the light of previous research the presented results can be interpreted as providing some of the first evidence for influences of altered processing of social cues on cold cognition in SC. Schizophrenic patients are impaired in using social information as displayed by the eye-like stimuli to direct their spatial attention and in consequence guide behavior. This interpretation is further supported by the findings of Nestor et al. [21], that inhibition of return is specifically influenced by

gaze-cueing but not through other spatial cues in schizophrenic patients. Another experiment [36] has shown that gaze direction as irrelevant stimulus property may influence the ability to estimate the distance between two schematic persons running away from each other. Healthy controls estimated the same distance as being bigger in the condition where gaze was directed away from each other than in the condition where the two schematic persons looked at each other. In schizophrenic patients this effect was not present. Thus again gaze, being an irrelevant stimulus property, showed greater effects in healthy controls than in patients with schizophrenia.

In contrast, schizophrenic patients perform as well as healthy controls in gaze discrimination to the left or right, but experience difficulties, when gaze is directed towards them [18], or when gaze is deviated from the midline with 30 degrees [19]. Different from our experiment, gaze deviation was a task relevant stimulus property.

Thus it seems that schizophrenic patients are able to discriminate gaze directions in most cases correctly, but that their ability to use gaze deviation as an implicit, irrelevant stimulus property is impaired. Several authors [1, 13, 16] suggested that an "eye-direction detector" [37] is relevant in order to get the observed advantage found in the eye-like condition. Neuroimaging findings [38, 39] suggest multiple regions involved in gaze processing, 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 in an FMRI study differences in BOLD signal changes has been found in these two regions in schizophrenic patients compared to healthy controls [40]. It has therefore been hypothesized, that schizophrenic patients have a deficit in superior temporal sulcus function.

However, in a broader framework, cognitive control mechanisms are involved in the Simon task. Our results gives support for a deficit in cognitive control mechanisms in schizophrenic patients when only taking effects of the square condition in to account, but results of the eye-condition points in another direction. Thus we hypothesize that cognitive control mechanisms during the Simon task are differentially influenced by type of stimuli. Effects of gaze seem to be stronger than impairments of cognitive control leading to a small Simon effect in patients. Thus, our results point to an important interaction between social cues and cognitive control because we observed specific impairments in the "social" Simon task, rather than general impairments of cognitive control.

There are some 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 [1]. However, the decrease of the Simon effect in the patient group together with an increase in Simon effect in the group of healthy controls comparing the first with the second session does not support a general learning effect.

In conclusion, we found that early attentional processes are differentially influ-

enced by eye-like and geometrical stimuli. Patients are less distracted by deviated gaze in their response selection, especially, when gaze is directed to the side where response is expected. Thus the present study supports earlier findings of impairments of social cognition. Crucially, we demonstrate that this deficit in social cueing affects early attentional processes in schizophrenia. The combination of tasks examining different domains of social and core cognitive functions could shed more light into what extent the different domains may interact and to develop training programs with sufficient ecological validity.

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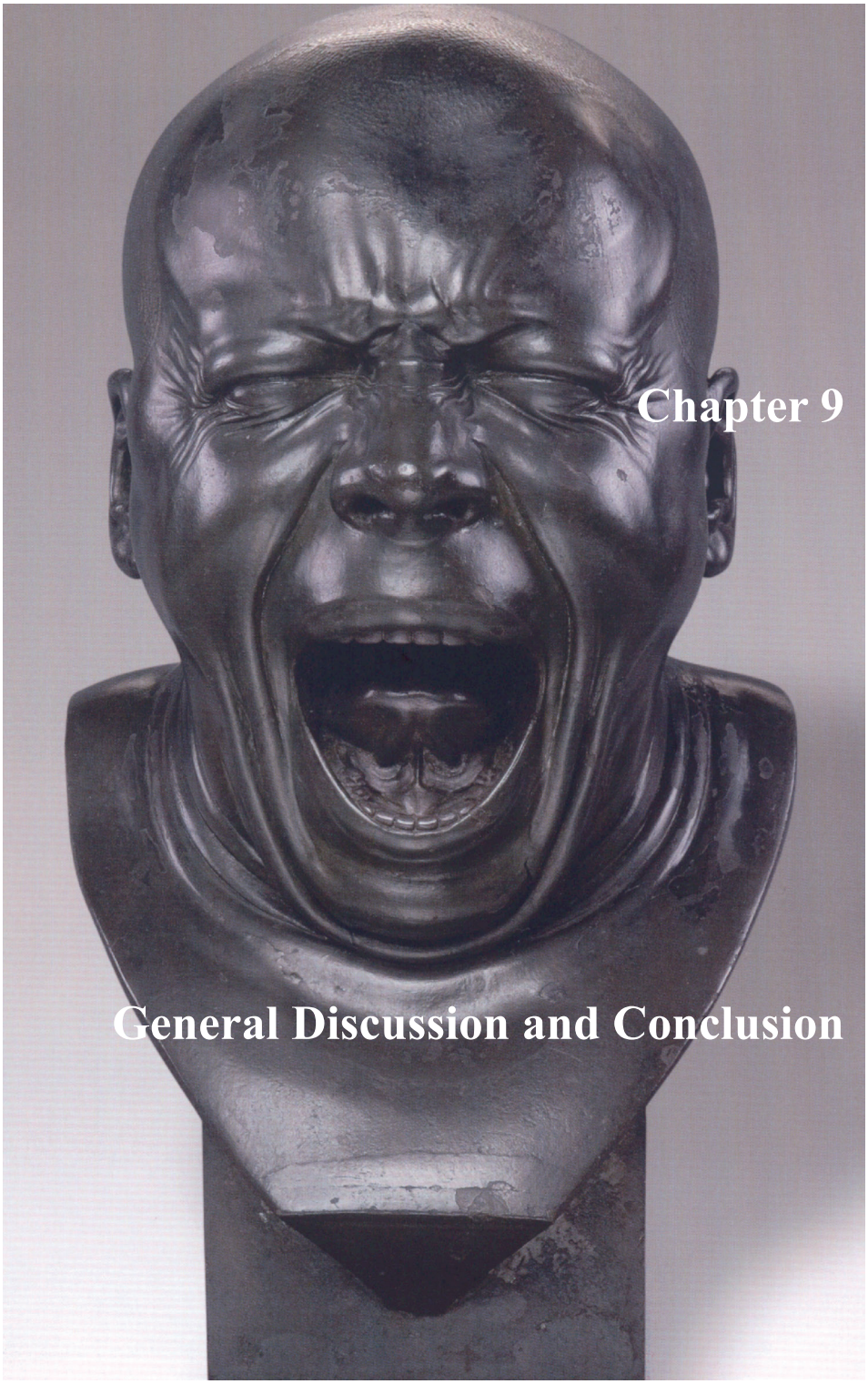

Chapter 9

General Discussion and Conclusion

ἐγὼ γὰρ δὴ οὔτε μέγα οὔτε σμικρὸν ξύνοιδα ἐμαυτῷ σοφὸς ὤν.

Plato, ΑΠΟΛΓΟΓΙΑ ΣΩΚΡΑΤΟΥΣ

The aim of this thesis was to shed more light on the additive, interactive or even inhibiting effects of emotion on cognition and vice versa. The answers that were found also raised many new questions concerning the relationship between these fundamental conditions of the human psyche. And this is true for both healthy controls and patients with schizophrenia.
As this thesis is intersected by the research techniques employed (FMRI vs. pure behavioural research) and the participants studied (healthy controls only vs. healthy controls and patients with schizophrenia), the general discussion is also intersected in several parts. At the end, general conclusions will we presented
With respect to the topics that are part of this thesis, I will focus on five topics, the influence of emotion on pain perception, working memory, attention, error processing, and social cognition.

Neuroimaging studies

Pain and emotion

In chapter two we examined the processing of painful and non-painful stimuli during different states of consciousness. One of these was supposed to mimic a state of severe dissociation.
Hypnosis shares features of dissociation, such as reduced attention for extraneous stimuli, increase in absorption and a reduction of spontaneous thoughts [1, 2]. Both states also comprise a detachment from emotional experience [2], but in hypnosis next to the relaxation induction specific suggestions are necessary to induce an effect similar to depersonalisation [3, 4]. Thus, hypnosis can be used to simulate the dissociative state, when adequate suggestions are used, which modulate perceptual and emotional experience associated with the processing of painful stimuli.
This has been done in the study described in chapter two. In contrast to the suggestion used in the experiments by Rainville [5] and Hofbauer [6] the hypnotic suggestion did not directly target the experience of pain but intended to mimic dissociation. Hypnotic relaxation did neither change the subjective experience of pain, nor the observed brain activity reflected by the changes of BOLD-signal. In contrast, the additional suggestion to induce an out-of body experience, resembling the state of depersonalisation, reduced BOLD-signal in primary sensory regions, and parietal brain regions associated with body representation in the brain. Lesions in these regions have been found to cause spatial neglect [7]. In addition, the amygdala showed reduced BOLD-signal compared to the awakening condition, suggesting a reduced experience of negative emotion evoked by the painful stimulus. In summary, the results suggest that the symptoms induced by dissociation are accompanied by changes in several brain regions, which explain the reduced experience in pain. Similar results can be achieved by modulation of emotion by odours [8] or pictures displaying emotional contents [9-11]. Both manners of inducing emotion affect regions associated with the sensory and the affective dimension of pain, an effect that needs further examination. One may

suggest that emotional stimuli also recruit attentional resources [11], which affect sensory brain regions. Another explanation could be that the separation in a sensory and an affective dimension of pain processing is not as sharp as it initially has been suggested.

Our study extends the understanding of mechanisms of hypnosis in the experience of pain. Using a specific suggestion, brain structures involved in both sensory and affective processing of pain can be influenced, and are associated with a reduction in pain perception. In addition, the suggestion "to feel outside your own body" can be used as a model of depersonalisation and may explain, why patients do not feel pain when inflicting self-injury in a state of depersonalization. However, this study can only present a model, which has to be further validated in patients. One of the most important limitations of our study is the small number of participants, thus a replication in a greater number of subjects is desirable. Depersonalisation involves both changes at the pure perceptual level and at the emotional level. Thus, another limitation of our study is that the suggestion that was used can not differentiate sufficiently as to what process is leading in the reduced experience of pain, emotional numbness or the changed perception of the physical features of the pain stimulus. Additional studies using different types of suggestions would be useful to investigate the differential effects of depersonalisation more thoroughly. Furthermore, the investigation of patients, who experiences depersonalisation, with a similar design is necessary to falsify or verify the conclusion made in our study.

Emotional Working Memory

In animal research, the lateral prefrontal cortex [12] and the parietal cortex [13] have been found to play an important role in working memory (WM). In humans, working memory is a widely examined neuropsychological function examined with FMRI. Indeed the above-mentioned regions show increased BOLD-signal during working memory performance using delayed match to sample paradigms [14, 15] or N-back paradigms [16, 17]. A meta-analysis of neuroimaging studies of working memory published several years ago [18] found additional to these two brain regions more regions in the occipital and temporal lobe that are associated with the successful performance of working memory tasks. According to Wager et al. [18], the increase in BOLD signal in certain regions depends on the material of the task (spatial, object, verbal) or differences in task demand (pure storage vs. manipulation during delay). Most, but not all regions, have higher BOLD signal increases during paradigms that put demands on executive functions.

Working memory for faces forms a subcategory of object working memory. In chapter three, we examined healthy volunteers with FMRI to identify brain regions associated with emotional WM. After some early papers [19, 20] examining working memory for faces, renewed interest in this research questions arose with upcoming neuroimaging [21-26]. These studies mainly focused on the question

whether specific regions could be detected for facial working memory. During the maintenance of faces, changes of BOLD signal were found in the inferior and midfrontal gyrus when compared to spatial information [23] and in the superior frontal gyrus and the intraparietal sulcus when compared to voices [27].
Apart from our study presented in chapter 3, two other studies examined facial working memory for identity versus emotional expression [28, 29]. Both studies differed with respect to ours in their design, using either a N-back task [29] or lacking a parametric increase of stimuli in a delayed match to sample task [28]. Increased BOLD-signal for the emotion compared to the identity condition were found in the orbitofrontal cortex during encoding and retrieval [28], and in the inferior frontal gyrus and the superior temporal gyrus [29]. The amygdala showed a general effect for faces, but did not differentially react to the emotion compared to the identity condition [28]. Most of these regions have been described earlier in the processing of emotional compared to neutral faces [30]. In contrast to both studies, we found differences of BOLD-signal in the amygdala, during maintenance in the comparison of the identity or the emotional expression of faces. However, contrary to our expectation BOLD-signal was higher in the identity condition.
Studies, which examined short-term memory for faces, found increases of BOLD-signal in the right superior temporal sulcus [24, 31] the right inferior frontal lobe [24, 31] and the right globus pallidus [24, 31] for emotional compared to neutral faces. Increased BOLD-signal was found in the right extended amygdala for angry compared to neutral faces [31].
In summary, it seems that in WM tasks with emotional faces similar structures are involved as for the perception of emotional faces [30, 32]
Our study used a WM task with parametric load variation and an explicit task to encode and remember either facial identity or emotional expression. We demonstrated in the direct comparison of the two conditions that during the maintenance phase areas of the limbic system are involved, namely the right amygdala. Importantly these differences cannot be attributed to performance differences, as accuracy did not differ between conditions. However the stronger increase in BOLD-signal for the identity compared to the emotion condition was in the opposite direction as expected. Increased BOLD-signal in the amygdala during maintenance has also been found by LoPresti et al. [28], but without differences between the emotion and identity condition.
As in our study, other authors [28, 29] found no emotion modulated BOLD-signal in regions typically involved in WM tasks as the dorsolateral prefrontal or the parietal cortex.
Thus we extended the literature about the involvement of limbic structures in memory processes, which seems to be not only relevant for long, but also for short term memory processes, especially during maintenance processing in working memory. In addition, our study in accordance with previous studies shows evidence that the effects of emotional stimuli properties are processed in brain

regions, which are not part of the WM network.
One of the limitations of our study is the lack of a neutral control condition, which could have allowed examining the underlying processes of WM for emotional faces in more detail. Another limitation is that due to the ambiguity of the load 1 condition one third of our data could not be used for the analysis. The small number of participants did not allow distinguishing between males and females, which would be of further interest. Finally, due to our study design, we could not differentiate whether behavioural and/or FMRI results are less or more influenced by specific emotions.

Performance monitoring
Electrophysiological studies have consistently demonstrated that external feedback stimuli signalling an error evokes an event-related potential, called the Error Related Negativity (ERN) [33, 34] or Feedback Related Negativity (FRN) [35]. Source analysis has allocated the dorsal part of the ACC as the generator for the ERN. However, neuroimaging studies have demonstrated divergent results with respect to BOLD-signal change in this brain region, increased BOLD-signal [36-38], no BOLD-signal changes at all [39], or no differences between positive and negative feedback [40, 41].
In chapter four, we examined different types of feedback during a time estimation task, verbal feedback (good, bad) and facial feedback (happy and fearful expression). We hypothesised that facial feedback would increase the feedback-related BOLD signal by its higher ecological validity compared to verbal feedback, and that the BOLD-signal for feedback followed by a correct adjustment of time estimation would be higher compared to feedback followed by an incorrect adjustment.
In contrast to other studies, negative feedback did not increase BOLD-signal compared to positive feedback. We even found an increase of BOLD signal for positive feedback. Faces did increase BOLD-signal in the extrastriate visual cortex compared to letters. Effects of feedback were found in three additional areas; positive feedback caused stronger BOLD-signal increase in the amygdala, the fusiform gyrus and and the nucleus accumbens (NA). The NA is associated with the processing of reward [42, 43], while the amygdala is mostly associated with the processing of negative emotion [44, 45]. However, some studies have shown,that the amygdala may show stronger BOLD-signal increase for happy faces, depending on attentional demands [46] or mode of presentation [47]. One of the difficulties of the paradigm was that negative feedback was not informative with the respect to the direction in which behaviour had to be adapted. The comparison of negative feedback followed by a correct adjustment of time estimation with negative feedback with incorrect adjustment showed increased BOLD-signal in the RCZ for feedback with correct adjustment. Similar effects were found in the pre-SMA region. Thus, activation in the RCZ is not necessarily associated with negative feedback per se, but only with negative feedback causing a cor-

rect adaptation of behaviour. This interpretation is supported by a further study, which varied the initial paradigm by adding information to the negative feedback in which direction (longer/shorter) of the adaptation is necessary to improve the time estimation [48]. Here the RCZ showed an increase to valid compared to invalid feedback, suggesting that the RCZ is associated with the evaluation of the importance of the feedback stimulus. In addition, both studies found the amygdala more involved for faces [49] and for positive feedback [48, 49]. We suggest that the stronger increase of BOLD-signal to positive feedback, found in our study, is caused by the uncertainty elicited by negative in contrast to positive feedback. Negative feedback did announce insufficient time estimation, but did not give a clue as to which direction the estimation had to be changed to improve the result. In conclusion, it remains unclear to what extent emotional modulation influences the structures involved in performances monitoring.

Thus, the finding that the processing of positive feedback involves the rostral cingulate zone and the amygdala extends the literature of feedback processing and reinforcement learning. Increases of BOLD-signal to negative feedback followed by an improvement of time estimation suggest that more brain regions are involved in successful reinforcement learning, especially with respect to behavioural changes due to the feedback signal.

One of the limitations of our study is that negative feedback did not indicate in what direction behaviour had to be adjusted, which may have weaken the negative feedback signal in the rostral cingulate zone. Although male and female participants were investigated, groups were too small to check for sex differences, especially for the facial stimuli. At least we cannot exclude that the verbal feedback 'good' and 'bad" also elicited some emotional reaction.

Attention and emotion

In chapter 5 we examined the differences between task related and love related attention in a visual FMRI oddball experiment. Target detection has been found to increase BOLD-signal in a great number of cortical and subcortical brain regions. When emotional, predominantly negative, stimuli were used either as novel or as target stimuli, BOLD-signal increases were found most consistently in the ACC [50-52], but also in the amygdala [51-53] and frontal brain regions. We used pictures from either beloved persons or good friends of participants either as target or novel stimuli to examine the differential effects of task and love related attention. Task related increase in BOLD-signal was found in brain regions described earlier, and love related activity was found on trend level in the ACC. Putamen and caudate nucleus displayed increased BOLD-signal to pictures of the beloved when they were attended. Both regions have shown increased BOLD-signal, when participants passively viewed pictures of a beloved person [54, 55], and are associated with goal directed behaviour [56, 57]. However, we did not find increased BOLD-signal in these regions due to love only, but only in the interaction between task and love. Thus, our findings suggest that both emotional and

cognitive (attentional) processes are involved in goal directed behaviour associated with love.
Our study adds further evidence that love is better defined as a motivational state than an emotion. We showed that this motivational state is modulated by attention, as increased BOLD-signal is only present in the condition of the beloved person as a target. In addition, we showed that regions associated with the motivational state can also be induced even when the picture of the beloved is presented very shortly and embedded in a stream of standard faces and distractor stimuli. However, these effects are only found in a ROI-analysis, which limits the strength of our findings. This may be caused by a small number of participants that also impedes a separate analysis for female and male subjects. From our study, it cannot be referred that this motivational state and its neural correlate is solely triggered by romantic love or also by other stimuli inducing a motivational state.

FMRI and emotion cognition interaction
In the last years, several theories over the integration of cognition and emotion in the brain have been proposed. Dolcos and coworkers [58-60] hypothesized, mainly based on neuroimaging studies that there are two separable systems. On one hand, the "hot" ventral system, involved in the processing of emotions, which comprises the orbitofrontal cortex, the ventrolateral and medial prefrontal cortex, the occipitotemporal cortex, the amygdala and other medial temporal lobe structures. On the other hand, the "cold" lateral system, involved in cognitive/executive processing, which comprises the DLPFC and the lateral parietal cortex. Thus, certain brain structures are associated with specific functions, suggesting a categorical difference between emotional and cognitive processing in the brain. In this model, the detrimental effect of emotional distractors on working memory and the enhancing effect of emotional stimuli on long-term memory are both explained by a bottom-up modulation that origins in the medial temporal lobe. The amygdala is involved in both processes, enhancing hippocampal activity in the long-term memory task and inhibiting DLPFC activity in the WM task. In contrast, ignoring the emotional distractor, accompanied by better WM performance, is mediated by the top-down mechanism that origins in the lateral PFC. However, the limitation of this approach is that the studies, which are the basis for this theory, used only stimuli with highly negative valence, which were compared to neutral stimuli. Thus, this hypothesis covers only a small part of what can be summarized as emotional influence on cognition.
Pessoa [61] proposes a different view, mainly based on neuroanatomical and electrophysiological studies, suggesting a neural network model. In his theory, the difference between cognition and emotion is nearly abandoned, not at last because of the little agreement about what emotion is. Pessoa suggests that emotion and cognition always interact, and that therefore, separable brain structures for one or the other function are difficult to disentangle. Instead, he proposes a network theory, in which structures, commonly associated with emotion process-

ing like the amygdala, can act in cognitive tasks and vice versa. For example, the lateral prefrontal cortex shows not only increased activity for the cognitive demand of a task, but activity is at the same time modulated by a possible reward. In addition, Pessoa suggests that context plays an important role, causing a certain brain structure at one moment to be more involve in cognitive and at another moment to be more involved in emotional processing, or not to be involved at all at a specific moment. However, Pessoa admits that there may be differences between brain regions to what extend they are involved in multiple processes. Differences are based on the structural connectivity with other brain regions, the more a region is interconnected, the less its functions are specific for cognitive or emotional processing. Thus, brain regions associated with higher order processing are, following this approach, less specific than regions associated with early perceptional processing.

The proposal of Pessoa [61] receives support from a recent meta-analysis of neuroimaging studies aimed to examine cognition emotion interaction [62]. The authors described not less than 18 brain regions, which show a cognition-emotion interaction, ranging from frontal brain regions, over the basal ganglia, primary sensory area to the amygdala. Most of the regions overlap with regions also involved in cognitive control and to a smaller extent with regions involved in emotional processing. Furthermore, different brain regions are involved when emotion is task relevant or not, and a direct comparison between these two categories revealed that in tasks, in which emotion is not task relevant the DLPFC and the parietal lobe show stronger BOLD-signal changes.

When taking together the results from our studies, little overlap is found between regions that show an interaction between cognitive and emotional processing, suggesting that there are no specific brain regions, which process cognition-emotion interaction, independent from task or context. However, many of the regions, in which we detected interactions between emotional and cognitive processing, as the precentral gyrus (chapter 3), the precuneus (chapter 3), the middle frontal gyrus (chapter 4), the inferior parietal lobe (chapter 3 and 4) and the putamen (chapter 5), are also detected in the meta-analysis of Cromheeke and Müller [62]. In contrast, we did not find changes BOLD-signal as suggested by the theory of Dolcos and coworkers [58-60]. That does not necessarily contradict their theory, because the stimuli used in our studies differed substantially from the stimuli with high negative valence used in the original studies. The subtle differences between emotional faces, or between the identity of the beloved person and a good friend, and the variety of emotions, displayed in faces, could have caused that other brain regions were involved in our studies, than proposed in the model of Dolcos and coworkers.

Summarizing, our results are in better agreement with the neural network based theory of Pessoa [61] that suggest a state and context dependent involvement of brain regions in emotional and cognitive processing in opposite to the view of two interconnected brain system, one processing the “hot” emotions” and the

other processing "cold" cognition.

Behavioural studies in patients with schizophrenia

The main theme of the second part of this thesis is the modulation of cognition by emotion in patients with schizophrenia.

Working memory for faces with emotional expressions

In chapter 6 we examined working memory performance for either the identity or the emotional expression of faces between patients with recent onset schizophrenia and healthy controls. As control task participants accomplished a task, in which they had to match the same faces that were used in the WM task.

In contrast to the studies, which examined working memory for emotional faces [63-66], in the study presented in chapter 6 emotional expression had to be remembered explicitly, and working memory load was changed parametrically. In addition, we examined patients with recent-onset schizophrenia, of which nearly the half was antipsychotic-naïve and the remaining patients received relatively low doses of antipsychotics. This allowed to control for medication effects and to look for deficits already present in the early phase of the disorder. A further advantage to most previous studies was the control task we administered to control for visual impairments abstained from verbal recognition.

The results of our study supported the hypothesis that the processing of facial emotional expression and the performance of WM rely on different systems, as earlier suggested by the results of Linden et al. [65]. WM performance was impaired in patients and when emotional expressions had to be processed, both patients and healthy controls were less accurate. However, no interaction between the two effects was found. Furthermore, psychotic symptoms deteriorate the WM impairment, as antipsychotic (AP)-naïve patients were significantly more impaired than treated patients in WM performance, and had more positive symptoms. In addition, we found some evidence that perceptual impairments may underlie some of our results. AP-naïve patients performed at trend-level worse on the matching task than healthy controls. Whether this is an effect of visual perception impairments in a narrow sense as suggested by some studies [67, 68] or an effect of dysfunctional visual scanning of the faces [69], cannot be differentiated through our results, which limits the strength of our findings. Our results further suggest that psychotic symptoms but not negative symptoms are more relevant factor for the impairment in WM performance and processing of emotional faces in this early stadium of the disorder. We cannot exclude the possibility that the lack of matching patients and healthy controls for level of education is partially responsible for the observed results. However, the significant differences in accuracy in the WM task between the two patients groups assure us that this effect is based on factors related to schizophrenia and not the level of education.

Emotional modulation of attention with an adapted Stroop task

In chapter 7 we examined the influence of emotion on selective attention with an emotional Stroop task between patients with recent onset schizophrenia and healthy controls. The modulation of selective attention by emotional words does not differ between healthy controls and patients with schizophrenia. This finding is in accordance with two recent emotional Stroop studies in patients with schizophrenia [70, 71]. We extended their findings by investigating patients with recent-onset schizophrenia and a short duration of medication use. A third of patients were even free of medication. Patients had increased response latencies to all stimulus categories, but showed the same modulation of attention by negative stimuli as healthy controls. In contrast to the results of the working memory task, the results of the present study do not lead to a clear conclusion about the underlying systems responsible for attention and processing of emotion. On one hand, the increased response latencies point to a general reduction in speed of processing. On the other hand, attention to the relevant stimulus property is equally affected by negative emotional content in both groups. Recent theories [72, 73] suggest that the ability to experience current feelings is not impaired in patients with schizophrenia in contrast to the ability to experience of anticipatory or bygone feelings. Thus with respect to the results of our study, the lack of differences between patients and healthy controls could be explained by the short and intermixed presentation of emotional words from different categories, which evoke specific emotions only for a short period of time.

However, the results contradict two earlier studies [74, 75], which reported differences in interference due to emotional stimuli between patients and healthy controls. As described in the introduction of this thesis, differences could be explained by the different task designs (single trial vs. card version), which are suggested to require different cognitive operations [76]. Henik and Salo [76] suggest that the card version of the Stroop task increases the attentional demand, because besides the within-item interference (also present in the single-trial version) between-item interference is present. They suggest that patient with schizophrenia are impaired in narrowing down their attention to a single item within a cluster of items.

However, this model would not explain the differences reported in the studies two earlier studies. With regard to the emotional words, it seems more reasonable to suggest that the relevance of stimuli to individual psychopathology is more important. Bentall and Kaney [74] found the biggest increase in response latency for words with paranoid content in in patients with delusions, and the longest response latency in depressed patients for words with depressed content. This explanation is supported by that the fact that in patients with anxiety disorder the Stroop effect is most robustly evoked by emotional words related to the anxious thought content of participants and not by emotional valence per se [77].

A limitation of our study is that participants did not rate the stimuli with respect to valence or arousal. Whether the increased response latency to negative stimuli

is mainly based on valence or arousal evoked by negative, remain undetermined. Future research should take all these aspects into account. In a future task design, one could use individually tailored positive and negative words and compare them to standard emotional words. A second possibility could be a direct comparison of a single trial and a card version of the Stroop task using emotional words.

Social cognition and the Simon task

The last experiment focused on differences in social perception between healthy controls and patients with recent onset schizophrenia. Here, we used an adapted version of the Simon task, in which eye-like and rectangle stimuli were presented. Previous research in healthy controls [78] has found that the eye-like stimuli cause spatial coding and thus elicit a Simon effect, but the rectangle stimuli did not. Indeed, it seems that patients with recent onset schizophrenia are less influenced than healthy controls by gaze directed to the left or right. The Simon effect to eye-like stimuli found by Zorzi et al. [78] was not present in patients with recent onset schizophrenia, but in healthy controls in the same size as reported previously [78]. By that, we demonstrated that automatic processing of gaze is impaired in patients with schizophrenia, also in circumstances when gaze is irrelevant. We also showed that this is not due to a general perceptual deficit, because the rectangle stimuli influenced the response behaviour of patients, but not of healthy controls. This result seems to be in contradiction to the results of studies, which show that the perception of gaze is unaffected in patients with schizophrenia [79-82]. In addition, Akiyama et al. [83] reported that eye-like stimuli affected spatial attention in patients with schizophrenia, but the abstract stimuli did not. One of the underlying causes could be that gaze direction in our study is a non-relevant and by this an implicit stimulus property. Similar effects of implicit versus explicit processing of emotional stimulus properties have been described. For example, emotional modulation of memory seems to be less prominent, when an implicit memory task has to be performed [84]. On the other hand, for working memory [65] and selective attention (see results from the emotional Stroop task described above) cognitive performance is not influenced differentially by implicit emotions in patients compared to healthy controls.

A clear limitation of our study is that we did not use a standard Simon task as control experiment. By this, the specificity of the influence of gaze for the obtained results had been further tested. Especially taking into account that in the studies investigating IOR one study found a specific impairment for gaze [85], but others not [86, 87].

Emotion and cognition in patients with schizophrenia

As in the neuroimaging studies, no coherent effect of emotion on cognitive performance in patients with recent onset schizophrenia has been found in the studies we performed.

This is in accordance with the literature, which also showed contradictory results

for the emotional modulation of cognitive functions. Two reviews of emotional memory modulation [84, 88] reported a great variety of effects of emotion on memory with respect to the modulation of memory by emotion, but also with respect to group differences. In some studies memory for pleasant stimuli was diminished in patients compared to healthy controls [89], in others this was true for unpleasant stimuli [90] and there is also evidence that this is true for both kinds of stimuli [91].
Additional studies that examined emotional modulation within different domains of cognition, such as attention [92-94] and executive functions [95] did not find differences in emotional modulation between healthy controls and patients with schizophrenia. In addition, electrophysiological studies examining emotion recognition [96] or the impact of IAPS stimuli as novel/distractor stimuli in an oddball task [93], find no differences in the event related potentials related to the emotional stimuli between healthy controls and patients with schizophrenia.
Summarizing the results from our studies, there seems no general impairment of emotion cognition interaction in patients with schizophrenia. In fact, together with the existing literature impairments seems to rely on factors such as task instruction, task design, involvement of additional cognitive domains for successful task performance, involvement of executive functions and motivation. These aspects will be further discussed in the following section.

General Conclusion

The first and most important conclusion from this thesis and the literature referred to in the introduction and the general discussion is that the relation between cognition and emotion is much more complex as it seems at first glance. One of the most severe difficulties comes from the fact that emotion is a term covering so many different facets [61, 72, 97] that the simple use of the term 'emotion' in a scientific context seems to be problematic. At least the same is true, when using the term 'cognition'. Both terms describe a concept but not a specific function. Stating this, I must conclude that the main idea, to find an answer to the initial question formulated in the title of this thesis, has failed in the sense that this is a question, which cannot be answered in such a broad way. Thus, the question has to be more focused.
Several aspects of emotion need more attention. First at all, I think that the common use of differentiating emotions in positive and negative and less or more arousing does not cover the complexity of emotions. Of course, stimuli like the IAPS [98] can be categorized in this way, and it has been shown that stimuli differentiated by this approach cause different bodily reactions [99, 100]. Although it is possible to reduce different emotions on these two dimensions [101], this approach does not take into account the manifold of feelings human subjects experience. But this is also true for the concept of "basic emotions" [97, 102]. One solution to this problem could be, to investigate only specific emotions, but these have to be defined very well. That is not always trivial, as seen in our investiga-

tion of "romantic love", which seems not to be an "emotion" but a motivational state. Thus, as cognition is divided in several domains, which are well defined, different domains of emotion also have to be defined in such a way. However, as cognitive domains are not independent from each other, this will be also true for emotions. The definition of distinct emotions is much more difficult, not at last caused by the fact that our knowledge about the individual experience of an emotion relies on the verbal report, although emotions are often associated with bodily experiences and changes of facial and bodily expressions.

To overcome this problem, the recent proposal of LeDoux [103] with respect to animal studies in emotion research seems to be attractive. He proposes, to investigate behaviour, which is related to survival or the maintenance of homeostasis together with the associated somatic changes and brain circuits. In a second step, one could search for analogues between these findings and human behaviour. However, this approach seems an extended variation of behaviourism by eliminating the subjective aspect and replacing the "black box" of behaviourism by biological explanations. In addition, following this idea would reduce the variety of emotions to a small set, and would link them inherent to Darwinian model of emotion, with the focus on the advantage for survival.

A cognitive approach to emotion would incompletely solve the problem of the difficult definition of individual emotions. When emotions are defined by physiological reactions and their cognitive interpretations, the problem of the inner (experience and interpretation) and the outer (detectable somatic changes) world is not abandoned and neither, how these two aspects correspond to each other.

The complexity of this problem becomes clearer by the results of a study that was performed to investigate, whether emotional expressions of patients with schizophrenia and healthy controls would be rated similarly by a large group of students [104]. Posed emotional expression (less correspondence between subjective experience of emotion) were better recognized than emotional expression evoked by emotionally relevant autobiographical vignettes (higher correspondence between subjective experience of emotion) in both patients and healthy controls, but this effect was stronger in patients. As one may expect that evoked emotions would cause better recognisable expression, the opposite was true. This finding supports the suggestion that feeling and detectable emotion may diverge from each other

Another problem is that the time period, in which emotions are experienced, may play an important role. With respect to patients with schizophrenia, some recently published articles attended to this question. Roughly summarized, Strauss and Gold [73] suggest that patients with schizophrenia are able to experience current positive feelings in the same way as healthy controls, but are not able to keep them over time in the same way as healthy controls. One of the mechanisms they suggest to be responsible is an impairment in memory of contextual details of pleasurable situations, which facilitates the use of semantic memory and general beliefs, supposed to be less emotional that personal memory. Thus, a cognitive

impairment is the basis of the reduced feelings associated with past experiences or anticipation of future events, which in turn causes anhedonia. In a similar way, Anticevic and Corlett [105] argue that anhedonia and amotivation are caused by the inability to keep the subjective emotional experience in mind and translate them in to motivated behaviour, caused by WM impairments. Mano and Brown [106] also point to a deficit in working memory as a cause for impaired explicit processing of facial emotions. Further support comes from a recent review [84] about emotional modulation of memory, which reports that with increasing delay between encoding and retrieval emotional memory modulation is reduced in patients with schizophrenia.

Thus, it seems necessary to account for possible cognitive impairments in patients, when investigating processing of emotional stimuli. However, the results of the studies, which are part of this thesis, are in this regard heterogeneous. Working memory performance is not differentially influenced by emotionally stimuli in healthy controls and patients with recent onset schizophrenia. All participants were less accurate, when the emotional expression of faces had to be processed explicitly, suggesting a higher demand on perceptual differentiation of stimuli. On the other hand gaze induced spatial coding, expressed in a significant Simon effect in healthy controls, is absent in patients with schizophrenia, although stimulus complexity and thus the demand on perceptual abilities is much smaller than in the WM task. Whether these factors may also play a role in healthy controls needs further investigation.

An unresolved question remains, whether the rating of an emotional stimulus truly represents an experienced emotion. I already mentioned that as the "qualia" problem in the introduction. With FMRI it has been shown that the rating of a stimulus changed patterns of BOLD-signal compared to passive viewing of the same stimuli [107]. Rating of stimuli shifted BOLD signal from regions of the limbic system to regions associated with cognitive processes. Following the hypothesis of Strauss and Gold [73] patients could give similar ratings to emotional stimuli based on normative values, which not necessarily correspond to the subjective experience of the stimulus.

As a cognitive process never stands alone in the sense that the process is embedded in earlier acquired knowledge and actual perceptions, the same is true for emotional processes. In a recently published article Izard [97] proposes a framework, in which experienced and expressed emotion emerges out of a stream of on-going unconscious emotional and cognitive processes at the moment new derived information or perceptions are processed by the individual. In spite of the attractiveness of this theory, it will be difficult to disentangle these processes, not at last because of the inaccessibility of the unconscious stream of emotions and cognitions for the individual himself, but also for an external observer.

Future directions of research

Independent from the specific research interest, one of the most important needs for future research is the better definition which emotion is investigated. For this it is desirable to develop additional instruments, which helps to further characterize the emotion, for example the addition of psychophysiological methods during ratings, but also during neuroimaging experiments.

The individual impact of a specific emotion on a cognitive process has to be attended more thoroughly. For example, effects in the emotional Stroop task seems to rely on the individual relevance that emotional words have for participants. In this case, words, selected from a database for emotional stimuli, will not be evocative enough to effect selective attention.

In addition, it is necessary to take additional cognitive and perceptual processes into account. As it has been shown by several studies in patients with schizophrenia, perceptual and cognitive impairments are of relevant influence on the recognition of emotion.

Many studies investigating the influence of emotion on cognition focus on the immediate effect evoked by the emotional stimuli. But as cognitive functions can be differentiated by its temporal domain, for example selective versus sustained attention, short versus long time memory, these effects have gained less attention with respect to emotion. However, the model of Izard [97] predicts that also long term effects of emotion should be present, not only in disorders affecting emotion, such as anxiety disorders, depression and schizophrenia, but possibly also in healthy controls. Thus, the combination of mood induction and paradigms such as the emotional Stroop task, or emotionally modulated memory paradigms could be used to shed further light on the relationship between emotion and cognition.

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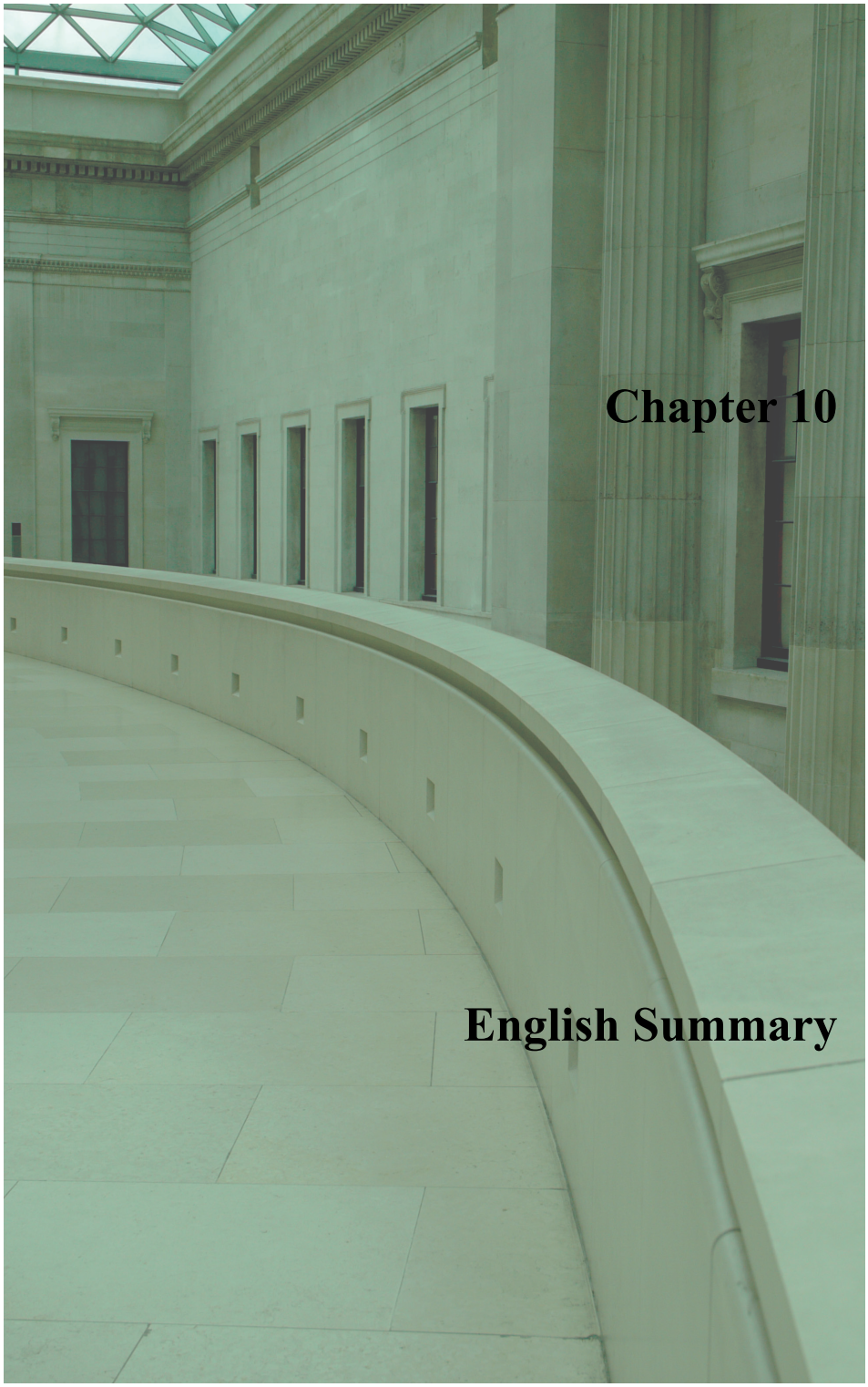


Chapter 10

English Summary

This thesis was started with the ambitious aim to gain some more insight in the interplay between cognition and emotion in healthy humans and patients with schiophrenia.
The first part contains several studies using functional MRI (fMRI) to examine the influence of emotion on perception, working memory, feedback processing and attention.
The second part comprises behavioural studies, which examines the differences between healthy controls and patients with schizophrenia in the influence of emotion on working and attention.

Chapter 2 describes an experiment which arose out of two observations, firstly, that hypnosis can be used to alleviate acute pain and secondly, that some patients with severe personality disorder report that they don't feel any pain when they automutilate. We therefore stimulated healthy participants with painful and nonpainful electric current in three different states of consciousness while performing fMRI to study the associated brain activity: 1. awake; 2. in hypnotic relaxation; 3. with the suggestion to be out-of their body; a simulation of depersonalisation. Because depersonalisation is characterised not only by a diminished perception of the "body-self" but also by numbness of emotional experience we were interested to what extent primary sensory and limbic regions of the brain were involved in the reduced experience of pain. Hypnotic relaxation alone did change subjective experience of pain only marginally and brain activation was not significantly decreased compared to being awake. In contrast, hypnotic induced depersonalisation significantly reduced subjective pain experience. Both the primary sensory cortex, representing the stimulated hand, and the amygdala showed reduced BOLD-signal change to the painful stimulus compared to being awake. In addition, an area in the parietal lobe, associated with the integrity of the body perceived as a whole, showed reduced BOLD-signal during hypnotic depersonalisation. This area has also been associated with "neglect", a neurological disorder characterised by either an impaired perception of the environment or even the own body. Therefore this may be a focus of further research in the origin of depersonalisation. In conclusion we could demonstrate that hypnotic relaxation is no enough to change subjective experience and brain activity of painful stimulation. To reach that, a hypnotic suggestion has to been given, for example hypnotic induced depersonalisation.

In chapter 3 we examined the influence of emotional stimuli on working memory. Many studies examining emotional processing with fMRI use pictures from the International Affective Picture System (IAPS) provided by Lang et al. However, these stimuli by themselves may cause significant differences in brain activation due to the variability of visual information besides there differences in emotional properties. Because of this, we chose to use faces with emotional expression as stimuli. In this experiment participants had to encode one to three faces displayed

sequentially and make a forced-choice decision whether a single face presented after 8 seconds matched with one of the previously presented faces. The faces to remember either displayed the same emotion in different persons or the same person displayed different emotions. We focused on the time span, in which participants had to maintain the faces previously encoded. To our surprise we found that the maintenance of faces displaying the same emotion (identity condition) led to a stronger increase of BOLD-signal in several parts of the limbic system than the maintenance of faces displaying different emotions (emotion condition). This result suggests that the limbic system needs a certain amount of information to build up stable representations.

In chapter 4 we present the results of the influence of faces with emotional expressions on performance monitoring compared to verbal feedback. During a time estimation task feedback about accuracy of estimation was given either via verbal (good - bad) feedback or via faces with emotional expression (happy and fearful faces). As in chapter 3 the results did not fit with our initial hypothesis. Firstly, the ecological more valid feedback (faces) did not show other patterns of brain regions with increased BOLD-signal than verbal feedback. Secondly, negative feedback was associated with higher BOLD-signal change in the rostral cingulate zone, while other studies reported this effect for negative feedback. However, BOLD-signal was in increased for positive feedback, which led to a better time estimation in the following trial, than negative feedback, which left behaviour unchanged in the following trial. Thus, activity of the rostral cingulate zone facilitates remedial action, but was not involved in error signalling as suggested from reinforcement learning theory.

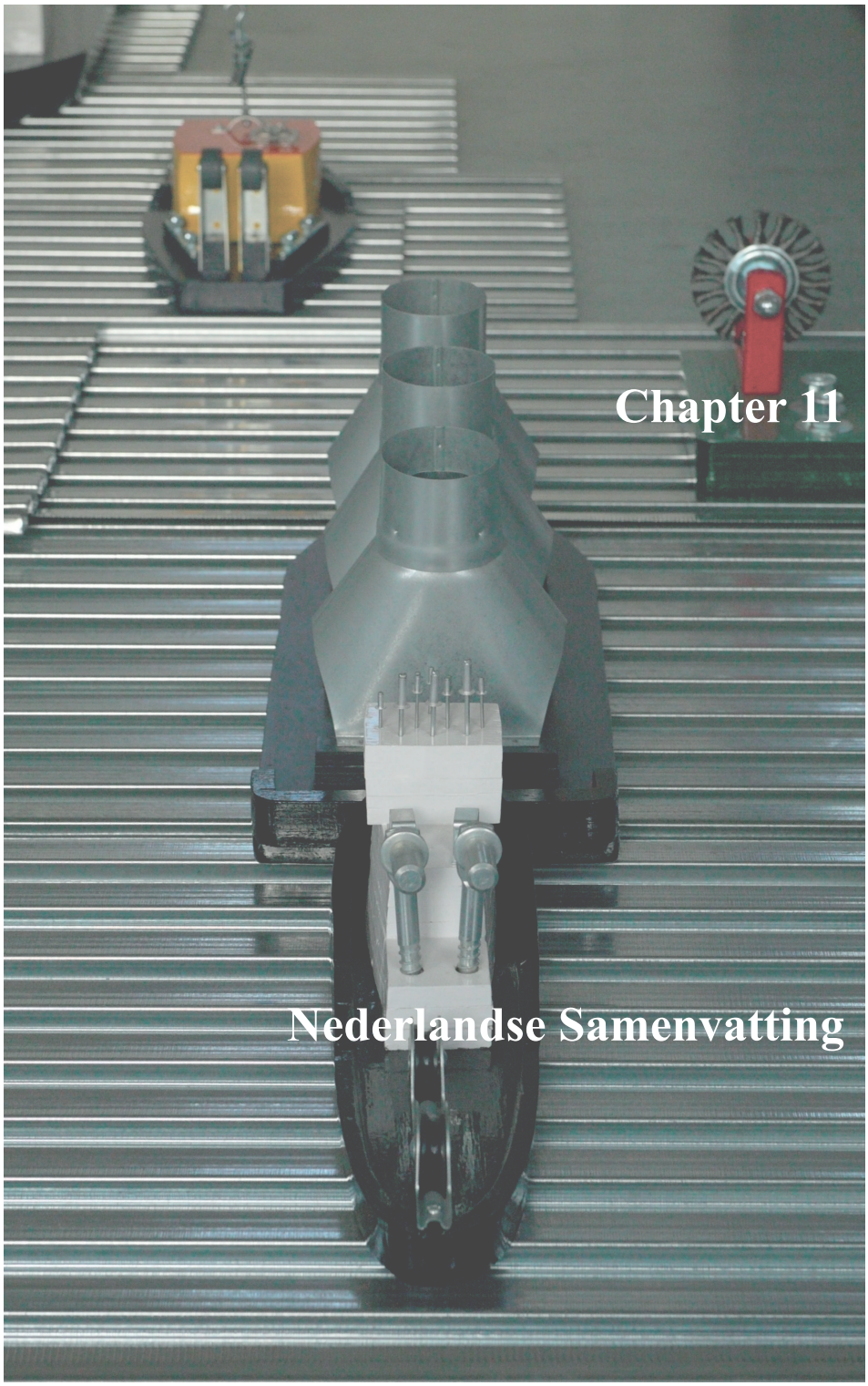
In chapter 5 we present the results of an emotional visual oddball task where pictures from a beloved person and a good friend were either used as target or as distractor. We examined, whether love as the suggested stronger emotion would led to a different pattern of brain regions with increased BOLD-signal than friendship, when the beloved or the friend were the target or distractor, respectively. Indeed in the dorsal striatum BOLD-signal was modulated in opposite directions. When the beloved person was the target BOLD-signal was increased compared to the friend, and when the beloved was the distractor, BOLD-signal was decreased compared to the friend. In addition, the difference in BOLD-signal between beloved and friend became smaller as the love and relationship lasted, suggesting that the dorsal striatum is especially involved at the time span of falling in love.

In chapter 6 we present the result of a behavioural working memory (WM) study in patients with recent-onset schizophrenia and healthy controls. The paradigm is similar to that used in the study presented in chapter 3. In addition to the WM paradigm a matching-task (MT) was introduced to control for possible perceptual deficits in the patient population, since they have more difficulties in the

detection of emotions in human faces. Nearly half of the patients had never used antipsychotics, therefor we split patients in two groups. Both patient groups performed worse than healthy controls in the WM task. All three groups performed worse when emotions instead of identity had to be memorized, but there was no interaction between the two conditions and group. In the matching task patients treated with antipsychotics performed as well as healthy controls while naïve patients performed worse than healthy controls. The results of this study suggest that impairments in WM performance and emotion recognition are independent from each other in patients with schizophrenia. However, psychotic symptoms seem to worse both impairments,.

In chapter 7 we present the results of an emotional Stroop task performed by patients with schizophrenia and healthy controls. The Stroop task measures selective attention by presenting words written in coloured letters. In the classic version colourwords as red, blue and green are written in letters with the same colour as the colour word (congruent) or in letters with a different colour (incongruent) and participants are asked to react on the colour of the letters, while ignoring the words. In the emotional version words with different emotional content (negative, neutral, positive) are used in addition to the colourwords. Typically participants show longer reaction times to the incongruent words, caused by an interference induced by the automatic tendency to read the word. We found that in addition to the classic Stroop effect both patients and controls showed a small interference effect for words with negative content. We therefore concluded that selective attention is modulated by emotion, but that this effect is not differentially present in patients with schizophrenia.

In chapter 8 we present the result of a study examining the influence of gaze on behaviour in patients with schizophrenia and healthy controls. For that purpose an adapted version of the Simon task was used. Typically, in the visual Simon task a stimulus is presented either in the left or right visual hemifield. Participants are asked to respond with their left or their right hand to a stimulus feature as the colour or form and to ignore the hemifield in which the stimulus is presented. The Simon effect describes the observation that participants react faster when the stimulus is presented in the hemifield in which the relevant feature corresponds with the response hand. In the adapted version eye-like stimuli were used which looked straight, to the left or to the right. The stimuli were either blue or green and subjects had to react to one of the colours with their left or right hand. While healthy controls showed a significant Simon effect for the eye-like stimuli, patients did not. We therefore concluded that patients are less likely to use social information to guide their behaviour, an important part of social cognition.



Chapter 11

Nederlandse Samenvatting

Dit proefschrift is begonnen met het ambitieuze doel meer inzicht te verkrijgen in het samenspel tussen cognitie en emotie in gezonde proefpersonen en patiënten met schizofrenie.
Het eerste gedeelte bestaat uit enkele functional magnetic resonance imaging (FMRI) studies, die de invloed van emotie op perceptie, werkgeheugen, het verwerken van feedback en aandacht onderzoeken.
Het tweede gedeelte bestaat uit gedragstudies waarin gezonde proefpersonen en patiënten met schizofrenie worden vergeleken op taken gericht op de invloed van emotie op aandacht en werkgeheugen.

Hoofdstuk 2 beschrijft een experiment dat voortkomt uit twee observaties; ten eerste dat hypnose acute pijn kan verminderen en ten tweede dat sommige patiënten met ernstige persoonlijkheidsstoornissen aangeven geen pijn te voelen als ze zich beschadigen. Wij hebben daarom gezonde proefpersonen in drie verschillende bewustzijnstoestanden met pijnlijke en niet pijnlijke stroomstoten gestimuleerd: 1. wakker; 2. in hypnotische ontspanningen 3. met de hypnotische suggestie zich zo te voelen alsof zij uit hun eigen lichaam zijn gestapt; een simulatie van het fenomeen 'depersonalisatie'. Omdat depersonalisatie niet alleen een verminderde waarneming van het eigen lichaam is maar ook met een emotionele 'verdoving' gepaard gaat, waren wij er vooral in geïnteresseerd, in welke mate primaire sensorische en limbische regio's van de hersenen betrokken zijn bij de verminderde ervaring van pijn. Hypnotische ontspanning veranderde de subjectieve ervaring in vergelijking met wakker zijn heel weinig en ook de hersenactiviteit was niet significant anders. Hypnotische depersonalisatie daarentegen verminderde de subjectieve belevenis van pijn significant. Zowel de primaire sensorische cortex voor het hand areaal en de amygdala hadden ten opzichte van de stimulatie tijdens wakker zijn vermindert Blood Oxygen Level Dependend (BOLD)-signaal. Daarnaast was er een gebied in de parietaal kwab met vermindert BOLD-signaal. Dit gebied wordt geassocieerd met de waarneming van het lichaam als een geheel en laesies in dit gebied kunnen een ziektebeeld genoemd 'neglect' veroorzaken. De rol van dit gebied in het ontstaan van depersonalisatie zou nog verder onderzocht kunnen worden. Samenvattend hebben wij laten zien dat hypnotische ontspanning onvoldoende is om de pijn belevenis te verminderen en de daarmee verbonden hersenenactiviteit. Daarvoor is een aanvullende suggestie noodzakelijk, zoals de door ons gebruikte. Hypnose kan worden gebruikt om bepaalde psychopathologische verschijnselen verder te onderzoeken. Aan de hand van het onderzoek kan worden gesteld, dat de verminderde pijn belevenis bij depersonalisatie berust op veranderingen van zowel de perceptuele als ook affectieve dimensie van de pijnmatrix.

In hoofdstuk 3 hebben wij de invloed van emotionele stimuli op het werkgeheugen onderzocht. Veel studies die emotionele processen met FMRI hebben onderzocht, hebben daarvoor stimuli uit het International Affective Picture System

(IAPS) van Lang et al. gebruikt. Een probleem van deze stimuli is, dat ze al door hun diversiteit aan inhoud en kleuren significante veranderingen in de hersenenactiviteit kunnen veroorzaken die los staan van de emotionele inhoud. Daarom hebben wij besloten emotionele zwart-witte gezichten als stimuli te gebruiken. In het experiment moesten de proefpersonen 1 tot 3 gezichten onthouden, die kort achter elkaar werden gepresenteerd. Na 8 seconden werd één gezicht gepresenteerd en de proefpersonen moesten aangeven of dit gezicht overeen kwam met één van de net gepresenteerde gezichten of niet. Wij hebben de focus van het onderzoek op de tijdsperiode gelegd waarin de gezichten moesten worden onthouden (maintenance). Wij vonden dat in deze fase de gezichten die dezelfde emotie hadden (identiteit conditie) leidden tot het stijgen van het BOLD-signaal in enkele regio's van het limbisch systeem in vergelijking met de te onthouden gezichten die verschillende emoties lieten zien (emotie conditie). Wij hebben daaruit geconcludeerd dat het limbisch systeem een bepaald hoeveelheid aan informatie nodig heeft om een stabiele representatie van deze inhoud op te kunnen bouwen.

In hoofdstuk 4 presenteren wij de resultaten van een studie naar de invloed van gezichten met een emotionele uitdrukking in vergelijking met verbale feedback op prestatie controle. Tijdens een tijdsschattingstaak werd de accuraatheid van de schatting of door verbale feedback (goed – fout) of door emotionele gezichten (blij – angstig) als feedback gegeven. Net als in hoofdstuk 3, waren de resultaten anders dan voorspelt.
De ecologisch meer valide feedbackstimuli (gezichten) lieten in vergelijking met de verbale feedback geen ander patroon van verhoogd BOLD-signaal zien in regio's die met feedback verwerking worden geassocieerd. Daarnaast leidde positieve feedback in vergelijking met negatieve feedback tot een hoger BOLD-signaal in de rostral cingulate zone. Maar het BOLD-signaal voor negatieve feedback was ook hoger als de tijdschatting verbeterde in de volgende poging, in vergelijking met negatief feedback waarop de tijdschatting niet veranderde of zelfs verslechterde. Wij concluderen daaruit dat activiteit in de rostral cingulate zone gedragsverbeteringen bevorderd maar niet altijd betrokken is bij het signaleren van fouten, zo als dit wordt gesteld door theorieën van het reinforcement leren.

In hoofdstuk 5 presenteren wij de resultaten van een emotionele oddball taak, waarin de gezichten van de geliefde en een goede vriend of als target stimulus of als afleidende stimulus worden gebruikt. Wij onderzochten of het gezicht van de geliefde tot een andere patroon van hersenactiviteit zou leiden dan het gezicht van een goede vriend, zowel wanneer het gezicht als target als wanneer het als afleidende stimulus wordt gebruikt. Ons hypothese was, dat liefde een sterker gevoel is dan vriendschap en daarom ook tot een verhoogd BOLD-signaal zou leiden. Wij vonden verschillen tussen de geliefde en vriend in het dorsale striatum. Onze hypothese was alleen correct voor het geval dat de geliefde persoon het target

was, en vice versa als de geliefde de afleidende stimulus was. Daarnaast, nam het verschil tussen geliefde en vriend geleidelijk af, naar mate de proefpersoon langer verliefd was of de relatie met de geliefde langer bestond. Hieruit hebben wij geconcludeerd, dat het dorsale striatum vooral een rol speelt in de vroege fase van verliefdheid.

In hoofdstuk 6 beschrijven wij de resultaten van een werkgeheugen studie, waarin patiënten met vroege psychose worden vergeleken met gezonde proefpersonen. De taak was een adaptatie van de taak, die in hoofdstuk 3 is beschreven. Wij hebben nog een controle taak toegevoegd, waarin gezichten moesten worden vergeleken (matching task), om voor stoornissen in de waarneming van gezichten te controleren. Omdat bijna de helft van de patiënten nog nooit antipsychotica had gebruikt, hebben wij de patiënten nog eens onderverdeelt in behandelde en onbehandelde patiënten. Alle twee patiëntengroepen hadden een slechtere prestatie op de werkgeheugen taak en alle proefpersonen presteerden slechter wanneer de emotionele uitdrukkingen moesten worden onthouden, maar er was er geen interactie tussen deze twee bevindingen. In het matching taak waren gezonde proefpersonen en behandelde patiënten even goed, maar onbehandelde patiënten deden het slechter dan de gezonde proefpersonen. De resultaten van deze studie wijzen erop, dat in patiënten met vroege psychose de beperking in werkgeheugen functie en het herkennen van emoties in gezichten twee onafhankelijke beperkingen zijn. Beide beperkingen lijken te worden versterkt door psychotische symptomen.

In hoofdstuk 7 presenteren wij de resultaten van een emotionele Stroop taak, die door patiënten met vroege psychose en gezonde proefpersonen werd gedaan. Met de Stroop taak wordt selectieve aandacht onderzocht, waarbij woorden geschreven in letters met verschillende kleuren, worden gepresenteerd en de proefpersonen worden gevraagd, een knop voor de kleur van de letters in te drukken, en de inhoud van het woord niet belangrijk is. In de klassieke versie worden kleurwoorden gebruikt zo als rood, groen enz. Als letters en woordinhoud hetzelfde zijn, is een stimulus congruent, als ze niet overeenkomen incongruent. De emotionele versie gebruikt daarnaast woorden met verschillende emotionele inhoud, om te onderzoeken of de emotie een invloed kan hebben op de selectieve aandacht. In het algemeen vertonen proefpersoenen langere reactietijden voor incongruente stimuli. Wij vonden daarnaast, dat gezonde proefpersonen en patiënten met een vroege psychose een significant langere reactietijd hadden voor woorden met negatieve inhoud, maar niet positieve woorden. Wij hebben daaruit geconcludeerd, dat selectieve aandacht wordt beïnvloed door de emotionele inhoud van woorden, maar dat dit alleen geldt voor negatieve woorden en dat dit effect niet verschilt tussen patiënten met vroege psychose en gezonde proefpersonen.
In hoofdstuk 8 presenteren wij de resultaten van een studie, waarin de invloed

van blikrichting op motorisch gedrag bij patiënten met vroege psychose en gezonde proefpersoenen wordt onderzocht. Daarvoor hebben wij een aangepaste versie van de Simon Taak gebruikt. In een typische Simon taak werden stimuli of in het linker of in het rechter blikveld gepresenteerd. Proefpersonen werden dan gevraagd, met de linker of de rechter hand op een eigenschap van de stimulus te reageren, zoals kleur of vorm (relevant), maar de kant (irrelevant) waaraan de stimulus wordt gepresenteerd te negeren. Als Simon effect wordt beschreven, dat proefpersonen sneller reageren als het blikveld waarin de stimulus in wordt gepresenteerd en de hand waarmee moet werden gereageerd, met elkaar corresponderen, dan als ze niet met elkaar corresponderen. In de aangepaste versie werden in plaats van geometrische figuren, op ogen lijkende stimuli in het midden van het scherm gepresenteerd, die naar links, rechts of het midden keken. Deze werden in twee kleuren gepresenteerd en proefpersonen moesten met een hand op de ene en met de andere hand op de andere kleur reageren. Gezonde proefpersonen lieten ook hier een Simon effect zien, maar patiënten met vroege psychose niet. Wij concluderen daaruit, dat patiënten minder goed sociale informatie, zoals blikrichting, gebruiken, om hun gedrag te sturen, wat een belangrijk onderdeel is van sociale cognitie.

Chapter 12

Dankwoord

Wie het leuk vindt, uren stil te liggen in een krappe buis, met periodes waarin je op een knop moet drukken als een plaatje verschijnt, en daarbij oorverdovende herrie op je afkomt en je tegelijk tegen het inslapen moet vechten, die is een geschikte deelnemer van een fMRI studie. Alle andere vinden het een marteling. Ik ben daarom alle deelnemers die het op zich hebben genomen mee te doen bij de verschillende fMRI studies heel erg dankbaar dat ze deze marteling op zich hebben genomen om het mij mogelijk te maken, dit proefschrift te presenteren. Niet minder dankbaar ben ik alle patiënten, die vaak de zin niet wilden zien, om mee te doen bij zo'n raar computeronderzoek. Vaak was de vraag "Is het verplicht", wat ik niet kon bevestigen, maar toch waren uiteindelijk veel bereid om hun tijd en moeite voor het onderzoek te geven. Zonder hen zou dit boek er niet zijn.
Op de tweede plaats wil ik Inge Bobbink, mijn vrouw, van harte bedanken, zonder haar zou ik nooit naar Nederland gekomen zijn en ook niet als psychiater bij Erasmus MC hebben gewerkt. Toen ik in "Deutsches Ärzteblatt" een advertentie las dat er psychiaters in Nederland worden gezocht, heb ik gesolliciteerd en toen ben ik bij BAVO terecht gekomen. Inge ging met mij mee naar het sollicitatiegesprek, wij zaten in een ruimte met drie mannen die de hele tijd rookten, blij dat ze in de enige kamer waren waar je dit nog mocht doen. Zij heeft mij daarin bevestigd dat ik naar iets anders moest kijken, als ik de indruk had dat ik daar niet gelukkig zou worden. En zo stonden wij op een dag aan de balie van de polikliniek psychiatrie en ik vroeg in het Engels of ik de baas mocht spreken. Ongelofelijk, maar de vrouw achter de balie, ik denk dat het Nienke was, die ging bellen, maar de baas was er niet.
Zo kom ik bij de derde die ik wil danken, prof. Michiel Hengelveld. Bij hem mocht ik dan op gesprek komen, nadat ik hem en email had geschreven en hij heeft mij daarna ook voor een officieel gesprek met een sollicitatie commissie uitgenodigd. Dat was iets heel nieuws voor mij, voor veel mensen te zitten, om uit te leggen, waarom ik bij hen wilde komen werken. Op dat moment spraak ik niet meer dan tien woorden Nederlands, maar ondanks dit gebrek, ben ik toch aangenomen, en ik wil mijn dank uitspreken voor het vertrouwen, dat in mij is gesteld om ook de taal voldoende te leren.
Ook mijn ouders wil ik graag danken, dat ze mij en ook mijn broers en mijn zus de mogelijkheid hebben gegeven ons naar ons interesse te ontwikkelen. Ze hebben ons geleerd nieuwsgierig te zijn, naar kennis te streven, en ze hebben ons ook de liefde voor kunst, literatuur en muziek meegegeven. Ik denk dat ze vaak bezorgd hebben gekeken, welke keuzes ik in mijn leven heb gemaakt en dat ze ooit een zoon zouden hebben die als psychiater ging werken, hadden ze zeker niet verwacht. Desondanks hebben ze er wel voldoende vertrouwen in gehad, dat ik mijn weg zou vinden, en hebben ze Inge en haar twee kinderen, Odine en Felix, direct als deel van hun familie gezien.
David Linden, heb ik voor het eerst ontmoet in 2000 op de FENS in Brighton, waar ik trots met een collega onze eerste fMRI studies heb gepresenteerd. Hij werkte toen in Frankfurt, waar ik kort daarna ook zou beginnen. Hij heeft mij

in mijn wetenschappelijke activiteiten vanaf deze tijd begeleid en ondanks dat hij ongeveer op dezelfde tijd wegging uit Frankfurt als ik is onze samenwerking blijven bestaan. Ik ben heel blij, dat hij ermee heeft ingestemd mijn promotor te zijn. Voor het geduld met mijn aarzelen, de lange tijd die ik altijd nodig had om mijn artikelen af te maken, wil ik hem bijzonder bedanken, en daar bovenop dat wij ook vrienden zijn geworden.

Freddy van der Veen, mijn copromotor, zonder jou was er geen fMRI studie ontstaan vanuit de afdeling psychiatrie. Hoewel onze interesses in het begin niet overeen kwamen, hebben wij toch enkele onderzoeken samen gedaan en ik heb van jou veel geleerd over de analyse van fMRI data. Jouw nauwkeurigheid heeft mij geholpen het grote doel niet uit het oog te verliezen. Helaas heb je op een moment de beslissing genomen weer bij je eigen peer-groep, de psychologen, te gaan werken, zodat er een einde aan onze samenwerking is gekomen. Maar ik hoop dat onze laatste gemeenschappelijke artikelen nog de waardering van reviewers ervaren, die ze naar ons eigen inschatting hebben verdient. Samen met jou is het gelukt een subsidie te krijgen, waarmee Sieds Dieleman het hier begonnen werk verder zou kunnen uitbouwen.

Sieds Dieleman heeft mij een groot gedeelte van mijn werkleven in het Erasmus MC vergezeld, eerst als oudste coassistent, dan als AIOS en later als promovendus. Lange tijd heeft hij samen met twee sociaal-psychitrisch verpleegkundigen, Odilia Streep en Wim Verveer, en mij de polikliniek voor patiënten met vroege psychose gedaan, waarbij wij nauw samen hebben gewerkt. Sieds heeft een grote bijdrage aan het onderzoek met patiënten geleverd en ook een belangrijke bijdrage bij de analyse en het opschrijven van de resultaten. Daarvoor mijn hartelijke dank verbonden met de hoop over niet al te lange tijd jouw proefschrift in handen te kunnen hebben.

Alle verpleegkundigen en overige medewerkers van de Unit voor vroege psychose van harte bedankt voor het geduld, dat jullie met jullie “Duitse” psychiater hebben gehad. In de tijd dat ik hier werk, is er veel verandert; veel van de medewerkers zijn naar andere plekken gegaan en van de oorspronkelijke structuur is door reorganisaties en de eisen van de zorgverzekeraars het een en andere verdwenen, wat het werken wel veranderde. Ondanks deze soms ongunstige omstandigheden hebben jullie steeds het onderzoek dat op de afdeling werd gedaan met alle krachten gesteund. Voor jullie werk heeft de familievereniging “Ypsilon” in 2011 de unit als de beste afdeling voor de behandeling van vroege psychose in Nederland onderscheiden, wat vooral aan het werk van de verpleegkundigen en de sociaal-psychiatrische verpleegkundigen te danken is.

Mijn collega’s psychiater, Marjolijn Bannink, Veerle Bergink, Anne-Marie van Hulst, Mijke Lambregtse - van den Berg, Esther Pluijms, Monique Raats, Sabine Roza, Nico van Beveren, Tom Birkenhäger, Paul Bouvy, Walter van den Broek, Jan Bruijn, Arthur van Gool, Witte Hoogendijk en Robert Jan Osse wil ik danken voor hun collegialiteit en steun. Duitsland en Nederland zijn buren, maar toch zijn er ook vandaag nog veel dingen vreemd voor mij, alleen omdat ik met een

andere televisie cultuur ben opgegroeid. Ze hebben mij geholpen, dingen in het gewone Nederlandse leven te begrijpen; of het mij gelukt is hun adviezen altijd op de juiste manier om te zetten, laat ik aan hun oordeel over. Ik zal nooit vergeten, dat vele van hen de inburgeringstest, die wij op internet deden, niet haalden. Daardoor voelden mijn tekorten in het dagelijkse leven veel minder erg.
Nico van Beveren was voor een lange tijd mijn directe collega op P1, hij stond altijd open voor een gesprek over patiënten, onderzoek en de wereld. Hij had de onstilbare drang mij met alle facetten van het Nederlandse leven kennis te laten maken, daarvan heb ik wel enkele dingen op gepikt, zoals "van Kooten en de Bie", Freek de Jonge, maar het "polderen" is mij steeds nog een beetje vreemd. Uiteindelijk hebben wij samen "Der Ring der Nibelungen" in de Amsterdamse Opera gezien, zonder hem had ik dat nooit gedaan, maar Duitser dan dit gaat ook weer niet.
Toen Nico weg ging, kwam Sabine Roza in zijn plaats, een moeilijke opgave. Ondanks haar vele andere taken, heeft ze de energie gehad belangrijke taken op P1 over te nemen, zoals de begeleiding van Odilia en Wim, de SPV van P1, en de dagbehandeling. En ze was en is er steeds voor overleg. Ik ben voor de tijd die ik met haar heb gewerkt heel dankbaar.
Voor Robert Jan Osse mocht ik in de afgelopen jaren altijd op woensdag de consultatieve dienst waarnemen. Dit was een welkome variatie van het overige werk en ik heb daardoor veel over de ziekenhuispsychiatrie mogen leren, ook door de vele discussies die ik met Robert Jan daarover heb gehad.
Anne Marie, Arthur en Jan zijn al een tijd weg van de afdeling, maar de verbondenheid met hen vanuit mijn eerste jaren bij de afdeling psychiatrie van het Erasmus MC is nog steeds groot, en ik vind heel fijn hen op congressen tegen te komen.

Een proefschrift is natuurlijk ook iets, waarmee je jezelf wilt bewijzen voor de wereld. Dat lukt soms beter, soms slechter, en dan kan een gedicht helpen, om deze wens te relativeren. Daarmee wil ik mijn dankwoord afsluiten.

IMMER

Immer einer behender als du

Du kriechst
Er geht
Du gehst
Er läuft
Du läufst
Er fliegt:

Einer immer noch behender.

Immer einer begabter als du

Du liest
Er lernt
Du lernst
Er forscht
Du forschst
Er findet:

Einer immer noch begabter.

Immer einer berühmter als du

Du stehst in der Zeitung
Er steht im Lexikon
Du stehst in Lexikon
Er steht in den Annalen
Du stehst in den Annalen
Er steht auf dem Sockel:

Einer immer noch berühmter.

Immer einer betuchter als du

Du wirst besprochen
Er wird gelesen
Du wirst gelesen
Er wird verschlungen
Du wirst geschätzt
Er wird gekauft:

Einer immer noch betuchter.

Immer einer beliebter als du

Du wirst gelobt
Er wird geliebt
Du wirst geehrt
Er wird verehrt
Dir liegt man zu Füßen
Ihn trägt man auf Händen:

Einer immer noch beliebter.

Immer einer besser als du
Du kränkelst
Er liegt darnieder
Du stirbst
Er verscheidet
Du bist gerichtet
Er ist gerettet:

Einer immer noch besser
Immer
Immer
Immer.

Robert Gernhardt (1937-2006)

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Curriculum Vitae

Christian Heinrich Röder, was born on September 18th 1963 in Limburg an der Lahn, Germany. He attended primary and secondary school in Limburg and graduated from Gymnasium in 1981. From 1983 till 1984 he fulfilled his civil service in a home of elderly persons. From 1985 till 1992 he studied Medicine at the Johann-Wolfgang-Goethe University in Frankfurt am Main, Germany. During his study he worked as teaching and research assistant at the Department of Anatomy and the Institute of Sex Research at the Johann-Wolfgang-Goethe University in Frankfurt am Main, Germany.

After graduating for his medical degree in 1992 he first followed a training in clinical neurology and from 1996 a training in clinical psychiatry. He is a board certified neurologist (Germany) since September 15th 1999 and a board certified psychiatrist (Germany) since April 25th 2001. He is also registered as psychotherapist (Germany) since April 21th 2004.

Since July 1st 2004 he works as psychiatrist at the early psychosis unit at Erasmus MC, Rotterdam. He actively participates in the training of medical students and residents in psychiatry and residents of other training programs.

He lives together with Inge Bobbink and her two children Odine and Felix.