Fachbereich Erziehungswissenschaft und Psychologie
der Freien Universität Berlin

Modulating Emotional Memories

Effects of Prefrontal Brain Stimulation and Oxytocin

Kumulative Dissertation
zur Erlangung des akademischen Grades
Doktorin der Philosophie (Dr. phil.)

vorgelegt von
Dipl.-Psych.
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Berlin, 2013

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Tag der Disputation:

08.05.2013

Acknowledgements

I would like to thank all the people who supported me throughout the course of my dissertation. My first thanks go to my supervisor Malek Bajbouj for entrusting me with challenging research projects, for his motivation, advice and help in developing my own scientific interests. Special thanks go to Simone Grimm for her continuous and invaluable support (sometimes essential for survival!), and for being a good friend throughout the years. My thanks go also to all co-authors and collaborators for their contributions to this work. I am especially grateful to Bruce Luber and Sarah Holly Lisanby for their fruitful collaboration.

I would also like to thank all colleagues and friends that made the lab a great place to work and have fun at the same time. Thank you for the unforgettable time in- and outside the lab!

And of course many thanks go to my dear family and friends for their encouragement at all times and for believing in me. Finally, I would like to thank Luca very much for being always close to me.

Contents

1 General Introduction

1.1 Emotional memory processing

Emotion can exert powerful effects on multiple aspects of memory, both at the behavioral and at the neural level. While a large body of research has demonstrated an emotional enhancement effect on episodic memory performance (e.g. Buchanan and Adolphs 2003; Kensinger and Corkin 2003; Smith et al. 2005), less is known about the relation between emotion and working memory.

Working memory refers to a limited capacity system that provides temporary storage and manipulation of information necessary for complex tasks such as comprehension, learning and reasoning (Baddeley 1986). One commonly utilized working memory task is the n-back task, which requires participants to decide whether the current stimulus matches the one presented n trials earlier. This paradigm involves a number of key processes within working memory including monitoring, updating and manipulating the remembered information (Owen et al. 2005). Numerous studies have shown that the prefrontal cortex, especially the dorsolateral prefrontal cortex (DLPFC), plays a key role in mediating working memory processes (e.g. Braver et al. 2001; Curtis and D'Esposito 2003).

The majority of studies investigating interactions between emotion and working memory have examined the influence of emotional state on working memory performance. Most findings revealed that negative mood decreases performance in working memory tasks, whereas no consistent effect was found for positive mood (e.g. Gray et al. 2002; Erk et al. 2007; Aoki et al. 2011). The impact of emotional content on working memory has been investigated only in a small number of studies, providing conflicting results. At the behavioral level, negative stimuli have shown both impairing (Kensinger and Corkin 2003; Lindström and Bohlin 2012; Perlstein et al. 2002) and facilitating effects (Lindström and Bohlin 2011) on working memory performance. Furthermore, improved task performance was found for positive stimuli (Perlstein et al. 2002; Lindström and Bohlin 2011). Other findings, however, revealed no impact of emotional content on working memory performance (Döhnel et al. 2008). At the neural level, no consistent relationship was found between activity of

the DLPFC and emotional stimuli in working memory tasks. While Neta and Whalen (2011) found DLPFC activity generally increased, Perlstein et al. (2002) reported right DLPFC function to be influenced by emotional valence, with positive stimuli enhancing and negative stimuli decreasing neuronal activity. In contrast, Döhnel et al. (2008) showed no effect of emotional stimuli on DLPFC activity. Furthermore, it is still unclear how working memory performance and associated brain activation is mediated by the properties of an emotional stimulus. One dimensional approach to emotion emphasizes the contribution of two orthogonal components, namely arousal and valence (Lang et al.1999; Russell 1980). Arousal refers to how strongly an emotion is experienced on a continuum that varies from calm to excitement. Valence refers to the subjective experience of the affective value or quality of an emotional stimulus independent of its sensory quality on a continuum that varies from positive to negative (Bradley and Lang 1994). Findings from neuroimaging studies linked arousal to neural activity in the amygdala and in the dorsomedial prefrontal cortex, whereas valence has been associated with neural activity in the medial prefrontal cortex and the lateral prefrontal cortex including the ventrolateral and dorsolateral prefrontal cortex (Dolcos et al. 2004; Grimm et al. 2006).

1.2 Integration of cognition and emotion

In attempting to localize brain functions, the prefrontal cortex has generally been implicated in playing an important role in cognition, while subcortical structures, such as the amygdala, ventral striatum and hypothalamus, are often linked to emotion (Pessoa 2008). Growing evidence of brain function and connectivity indicates, however, that “cognitive” and “emotional” brain structures interact at various stages of information processing, from encoding to retrieval (LaBar and Cabeza 2006). Moreover, Pessoa (2008) proposed that emotion and cognition not only strongly interact in the brain, but that they are often integrated in brain areas with a high degree of connectivity. The lateral prefrontal cortex, including the DLPFC, is an example of a brain region in which cognition and emotion are integrated. For instance, in a study by Gray et al. (2002), participants performed challenging working-memory tasks after watching short videos intended to induce emotional states. Remarkably, bilateral lateral prefrontal cortex activity reflected equally the

emotional and working-memory task components. The authors concluded that functional specialization is lost, and emotion and cognition conjointly and equally contribute to the control of thought and behavior. Other neuroimaging studies have provided further evidence for cognitive-emotional integration in the lateral prefrontal cortex (Goldstein et al. 2007; Perlstein et al. 2002). Although many current views of prefrontal cortex function tend to focus on its role in cognition, other prefrontal brain regions have also been considered to be involved in affective function. Figure 1 illustrates core (red areas) and extended regions of the emotional brain based on their appearance frequency in the affective neuroscience literature. Importantly, none of the regions can be viewed as “purely affective” (Pessoa 2008).

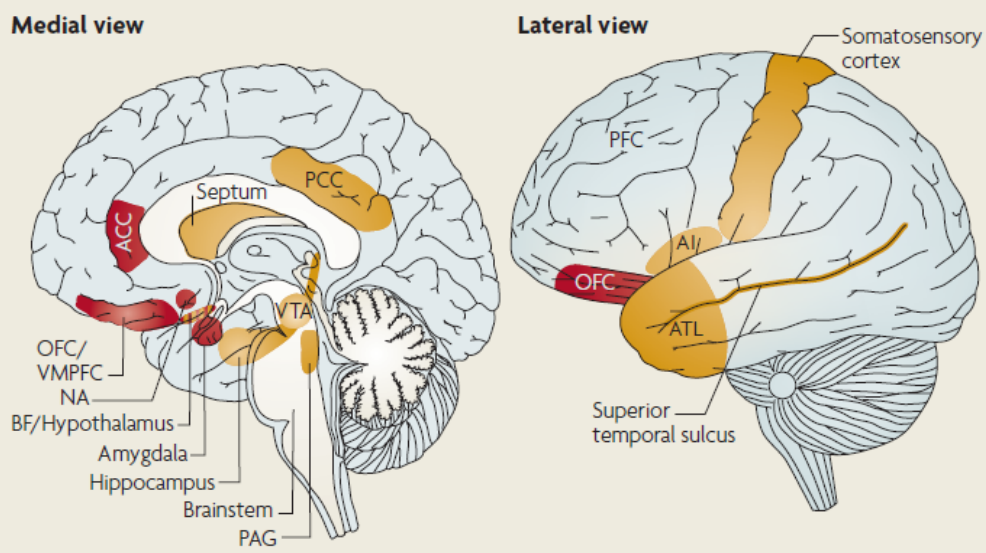

Fig. 1. The emotional brain: core and extended regions (Pessoa 2008).

ACC anterior cingulate cortex, OFC orbitofrontal cortex, VMPFC ventromedial prefrontal cortex, NA nucleus accumbens, VTA ventral tegmental area, PAG periaquaeductal grey, BF basal forebrain, AI anterior insula, ATL anterior temporal lobe, PCC posterior cingulate cortex.

1.3 Models of emotion lateralization

Different theories of hemispheric lateralization of brain activity during emotion processing have been proposed and are still under debate. The oldest theory is the right hemisphere hypothesis of emotion, which states that the right hemisphere is

dominant in processing all emotions, regardless of valence (Borod et al. 1998). In contrast, the valence hypothesis postulates that the right hemisphere is specialized for processing negative emotions, whereas the left hemisphere is specialized for processing positive emotions (Davidson and Irwin 1999). These two rival hypotheses were both supported by early research in patients suffering from unilateral brain damage as well as by studies examining divided visual field perception in healthy participants (for a review, see Demaree et al. 2005). Controversial findings continued to be seen in more recent studies using a number of different experimental approaches. However, evidence strongly supporting the valence hypothesis was derived from research using electroencephalography (EEG), associating relative increased left-hemisphere activity with positive emotional states and relative increased right-hemisphere activity with negative emotional states (e.g. Davidson 1992; Davidson et al. 1999). Accordingly, it has been shown that depressed patients show relatively less left than right frontal brain activity (Herrington et al. 2010). However, hemispheric lateralization of emotion processing may be organized along a dimension different from positive and negative valence as growing evidence indicates that the left prefrontal cortex also processes anger, a negatively valenced emotion that is associated with approach motivation (Fox 1991; Harmon-Jones 2003). Therefore, the frontal asymmetry of emotion has been related to a motivational direction model with the dimensions of approach and withdrawal rather than positive and negative emotions (Harmon-Jones 2004; Harmon-Jones et al. 2010).

1.4 Experimental Approaches

The following section describes the methods used to investigate and modulate emotional memories: Functional Magnetic Resonance Imaging (fMRI), the non-invasive brain stimulation techniques Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS), as well as the intranasal application of the neuropeptide Oxytocin (OXT). By using a variety of methodological approaches, this thesis aimed to provide a greater understanding of neural and cognitive mechanisms underlying emotional memories. We first used fMRI to identify cortical regions involved in a novel emotional working memory task (Chapter 2), followed by

a study using rTMS to further investigate the causal role of the prefrontal cortex in lateralized emotion processing (Chapter 3). In order to control for state-dependent stimulation effects, we performed a subsequent study and additionally applied prefrontal tDCS, which has been found to be an efficient preconditioning tool to influence rTMS effects (Chapter 4). Furthermore, we used a pharmacological approach and investigated oxytocinergic effects on emotional recognition memory (Chapter 5). Comparable to electromagnetic stimulation, the administration of OXT provides an emerging research tool to gain insight into brain mechanisms through the external modulation of cognitive-affective processes.

1.4.1 Functional Magnetic Resonance Imaging (fMRI)

Functional Magnetic Resonance Imaging (fMRI) provides a means of measuring local changes in brain activity. The underlying physiological principle is based on the close link between neuronal and metabolic activity (Roy and Sherrington 1890): when a brain region is activated, both blood flow and the oxygen content of the blood increase. fMRI allows neural activity to be visualized through changes in blood properties by using the different magnetic susceptibility of oxygenated and deoxygenated hemoglobin (Logothetis et al. 2001). Whereas oxygenated hemoglobin (oxyhemoglobin) is diamagnetic and is not influenced by the external magnetic field, deoxygenated hemoglobin (deoxyhemoglobin) is paramagnetic and conveys a signal that can be detected with magnetic resonance (MR) imaging (Ogawa et al. 1992). This MR signal is commonly referred to as Blood Oxygenation Level Dependent (BOLD) contrast. The BOLD effect arises because increased neural activity and related demand for oxygen result in an overcompensation of the vascular system with an increased amount of oxygenated hemoglobin relative to deoxygenated hemoglobin. Thus, by measuring changes in oxygen content of the blood, fMRI allows for an indirect measurement of activity in discrete brain regions.

The course of the BOLD signal (Fig. 2) illustrated by the ratio between oxy- and deoxyhemoglobin is known as hemodynamic response (HR). It varies according to the properties of the evoking stimulus and needs to be considered for the correct analysis and interpretation of fMRI data. Immediately after stimulus presentation, deoxyhemoglobin concentration increases transiently, leading to a decrease in the

HR function. After this initial “dip” (Hu and Yacoub 2012), the signal rises proportional to the underlying neural activity (Logothetis and Pfeuffer 2004) and peaks after approximately 5 sec. The signal reaches a plateau if the stimulus is maintained for a sufficient time. After the stimulus presentation, the signal returns to baseline, and eventually underpasses it. This “undershoot” effect (Buxton et al. 1998) is associated with a normalization of blood volume which is slower than the changes in blood flow, leading to relative high deoxyhemoglobin concentration (Jones et al. 1998).

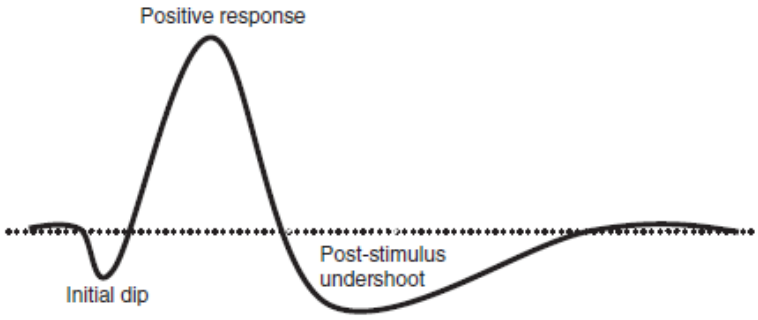

Fig. 2. Time course of the BOLD signal resulting from the hemodynamic response to neuronal activation (Hu and Yacoub 2012).

There are two basic types of fMRI studies: block design or event-related design (Donaldson and Buckner 2001). A block design separates the experimental task into distinct blocks, which are presented for an extended period of time. Brain areas of activation are identified by examining changes of signal intensity through comparison of the experimental condition with a respective reference condition. An event-related design presents discrete short events which are randomized for timing and order. Individual trials of tasks can be isolated allowing the contrast of activity associated with different trial types and the further investigation of the time course of BOLD signal changes under various conditions.

During the fMRI measurement, brain images are taken repeatedly and in sequence. A set of images covering a brain volume is typically acquired every 2-5 sec with a spatial resolution of 2–3 mm. The type of scanning technique most commonly used to obtain fMRI images is echo planar imaging (EPI; Schmitt et al. 1998). EPI enables the acquisition of images with a temporal resolution of up to 100 ms and therefore, allows the visualization of rapidly changing physiologic processes.

1.4.2 Transcranial Magnetic Stimulation (TMS)

Considering the correlational nature of studies using fMRI, Transcranial Magnetic Stimulation (TMS) provides a unique research tool to additionally investigate causal brain-behavior relationships in controlled experimental designs (Moser et al. 2002; Walsh and Pascual-Leone 2003). TMS can provide insight into separable neural circuits by non-invasive modulation of cortical activity (Pascual-Leone et al. 2000).

The essential feature of the technique is to use electricity to generate a magnetic field, which in turn produces electrical impulses in the brain (Barker et al. 1985). More specifically, the TMS device generates a large electric current which passes through a coil producing an alternating magnetic field. By applying a coil directly onto the head (Fig. 3), this rapidly changing magnetic field can penetrate the scalp and skull inducing an electric field sufficient to depolarize the underlying brain tissue (Pascual-Leone et al. 2000; Sparing and Mottaghy 2008). Although its precise mechanisms of action are still unclear, TMS is thought to activate the axons of cortical neurons and subcortical white matter (Ridding and Rothwell 2007; Sandrini et al. 2011).

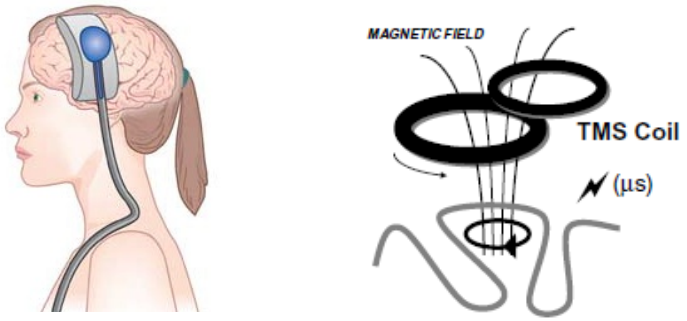

Fig. 3. TMS application (George and Aston-Jones 2010), based on the principle of electromagnetic induction of an electric field in the brain (Sparing and Mottaghy 2008).

To optimize the power and focality of the electric current, figure-of-eight coils are often used. In these coils, the current flows in opposite directions resulting in an electric field that peaks under the intersection of the two coil windings (Fig. 4a). Compared to figure-eight coils, circular coils have no focal maximum of current strength because the induced current declines towards the center (Fig 4b).

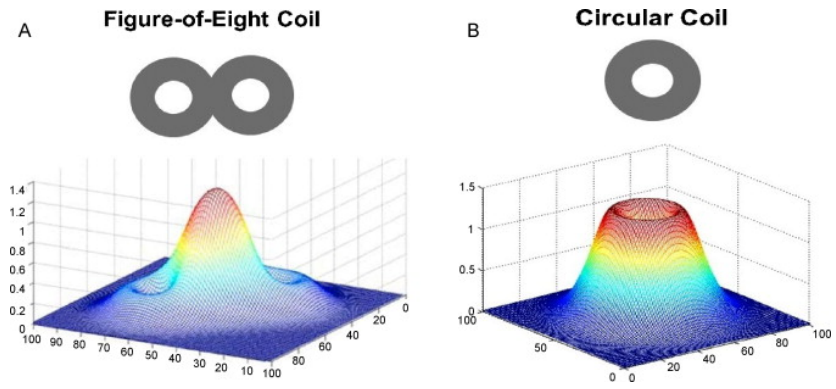

Fig. 4. a and b. Magnetic fields generated by a figure-of-eight coil and by a circular coil (Giordano et al. 2012).

Typical TMS devices can produce magnetic fields of 1,5 – 3 T. For a standard figure-of-eight coil with a maximum field strength of 2 T, the induced field peaks at about 2,5 cm from the surface of the scull. TMS can be applied as single pulses or as trains of pulses delivered at a fixed frequency (repetitive TMS, rTMS). In general, low frequency rTMS (~1 Hz) is capable of decreasing cortical excitability, whereas high frequency rTMS (5-20 Hz) increases it (Chen et al. 1997; Lisanby et al 2000). However, growing evidence indicates that stimulation effects strongly depend on the neural activation state in the targeted cortical region at the time of stimulation (for a review, see Silvanto et al. 2008). rTMS produces measurable after-effects lasting from minutes to hours (Thut and Pascual-Leone 2010), depending on the stimulation parameters such as the intensity, frequency, train duration and inter-train interval. The stimulation intensity is usually reported as a function of the individual motor threshold (MT) in order to account for differences in general cortical excitability. The application of rTMS is regarded as safe and without enduring side effects when following the recommended safety guidelines (Rossi et al. 2009; Wassermann 1998).

rTMS has become a standard brain stimulation technique for the noninvasive investigation of cognitive function (Pascual-Leone et al. 2000). Over the last decade, numerous studies additionally explored the therapeutic potential of rTMS for the treatment of a variety of psychiatric diseases (Fitzgerald et al. 2002).

1.4.3 Transcranial Direct Current Stimulation (tDCS)

In comparison to TMS, transcranial Direct Current Stimulation (tDCS) is a relatively simple method for modulating neuroplasticity. Unidirectional electrical currents are delivered constantly through two sponge electrodes soaked with saline solution, one serving as the anode and the other as the cathode (Fig. 5). Depending on the type of stimulation intended, one of the electrodes is placed directly above the area of interest in the underlying cortex. The other electrode is placed above a comparatively neutral area. The anode and the cathode are known to have opposite effects on the targeted brain region: Whereas anodal tDCS enhances cortical excitability, cathodal stimulation reduces it (Nitsche and Paulus 2000). The efficacy of tDCS depends on stimulation duration, the current strength applied in relation to electrode size, and the orientation of the current flow relative to the stimulated neurons (Nitsche et al. 2007; Datta et al. 2008). Stimulation is usually applied for a few minutes (up to 30 min) at intensities of 1-2 mA and can induce persisting changes in brain excitability for up to one hour (Nitsche et al. 2003; Fregni et al. 2006). The mechanism of action of tDCS is not completely clear but it seems to modulate the spontaneous firing rate of neurons by acting on polarity at the level of the cell's resting membrane potential (Sparing and Mottaghy 2008). As shown directly in animal studies, anodal stimulation results in a subthreshold depolarization, while cathodal stimulation hyperpolarizes neuronal axons (Scholfield 1990). tDCS can be applied safely with minimal adverse effects (Nitsche and Paulus 2000; Fregni et al. 2006).

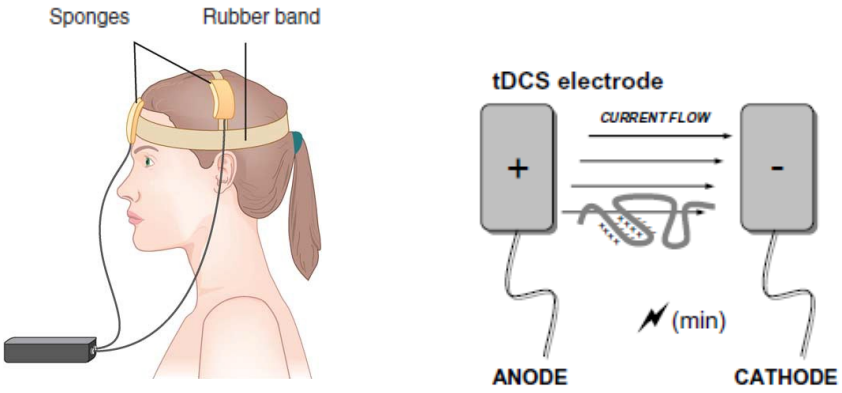

Fig. 5. tDCS application (Rosa and Lisanby 2012). The electric current flows from the anode to the cathode through the cortical areas (Sparing and Mottaghy 2008).

1.4.4 Oxytocin (OXT)

Oxytocin (OXT) is a neuropeptide with both peripheral and central functions (for a review, see Meyer-Lindenberg et al. 2011). After the synthesis in magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus, OXT is processed along the axonal projections to the posterior pituitary gland, where it is stored in secretory vesicles and released into peripheral circulation (Fig. 6). Though there are receptors for OXT throughout the body, its primary effects are in the uterus and breast, where it stimulates contractions and milk ejection. In addition, there is dendritic release of OXT into the extracellular space, resulting in local action as well as in diffusion through the brain to reach distant targets. OXT exerts its central effects via direct axonal connections from the parvocellular neurons of the hypothalamus to critical brain areas including the amygdala, hippocampus, striatum, suprachiasmatic nucleus (SCN), bed nucleus of stria terminalis (BNST) and brainstem. By acting as a neuromodulator, OXT influences the neurotransmission in these areas.

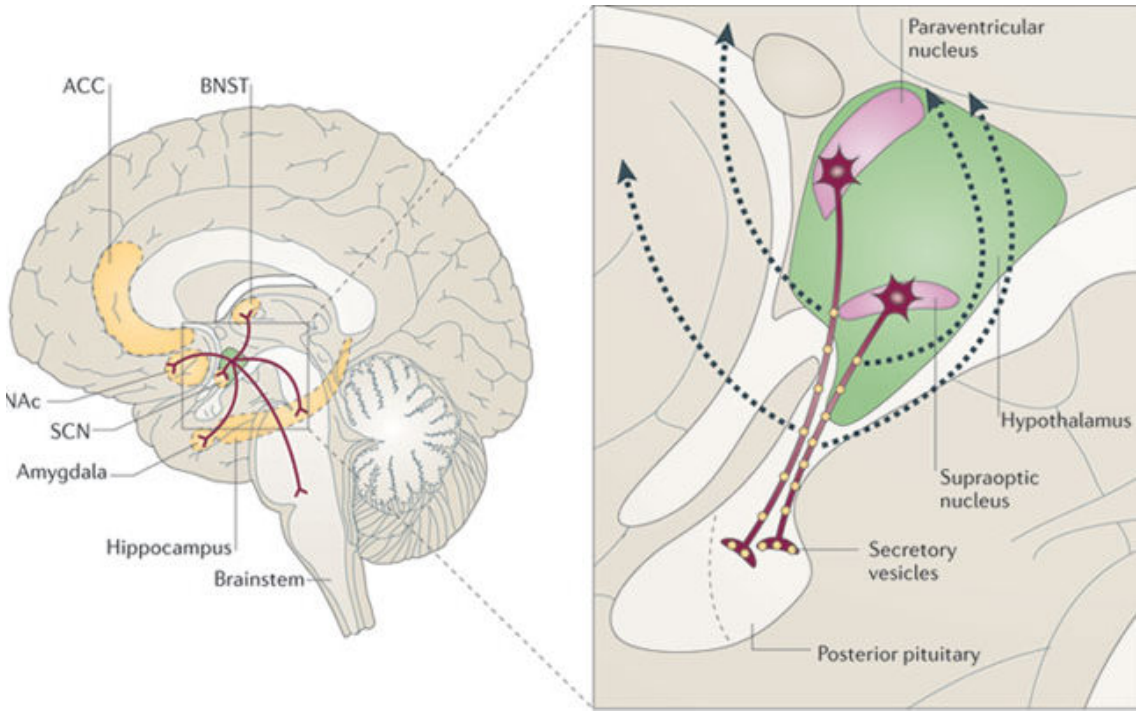

Fig. 6. Neurophysiology of OXT (Meyer-Lindenberg et al. 2011).

ACC anterior cingulated cortex, BNST bed nucleus of the stria terminalis, NAc nucleus accumbens, SCN suprachiasmatic nucleus.

OXT has been shown to affect a variety of human social behavior (for reviews, see Campbell 2010; Heinrichs et al. 2009). When applied intranasally, OXT improves emotion recognition for facial expressions (e.g. Averbeck et al. 2011; Di Simplicio et al. 2009; Fischer-Shofty et al. 2010; Guastella et al. 2010; Lischke et al. 2012; Marsh et al. 2010; Schulze et al. 2011), increases emotional empathy (Hurlemann et al. 2010) and facilitates trust in social interactions (Baumgartner et al. 2008; Kosfeld et al. 2005). Moreover, OXT has anxiolytic effects and diminishes both cortisol and behavioral responses to social stress (Heinrichs et al. 2003). Regarding the underlying neurobiological mechanisms, the amygdala might be a key structure for the mediation of the prosocial effects of OXT. fMRI studies showed a reduced activation of the amygdala in subjects receiving OXT when confronted with pictures of fearful, angry and happy faces (Domes et al. 2007; Kirsch et al. 2005; Riem et al. 2011).

The potential of OXT as an enhancer for specific processes involved in emotional memory, however, has been less clear to date. Studies using facial stimuli found both a memory-enhancing (Guastella et al. 2008; Rimmele et al. 2009; Savaskan et al. 2008) and a memory-impairing effect (Herzmann et al. 2012).

1.5 Aims of Research

The primary aim of this thesis was to investigate the effects of emotional content on working memory in healthy participants, at both the neural and behavioral level. We were especially interested in the role of emotional valence and arousal as well as in prefrontal hemispheric lateralization in emotional working memory.

In a first study, we developed a novel emotional working memory task (EMOBACK), a n-back task with standardized emotional words. This task provides a novel means of studying the interface between working memory and emotion. Participants underwent a fMRI session, in which they were presented with the EMOBACK task including positive, negative and neutral words from the Berlin Affective Word List (BAWL-R; Võ et al. 2009). Stimuli were matched according to different arousal levels in order to elucidate both valence and arousal effects.

Based on our fMRI data, we conducted a second study using rTMS to further investigate the causal role of the DLPFC in emotional working memory. In order to additionally explore hemispheric lateralization of emotion processing, selected EMOBACK stimuli were words assigned to the distinct emotion categories fear and anger taken from the Discrete Emotion Norms for Nouns - Berlin Affective Word List (DENN-BAWL; Briesemeister et al. 2011b). Based on a large body of research suggesting that anger is associated with approach motivation, anger-related stimuli allow the disentangling of positive emotional valence from approach motivational direction (Harmon-Jones 2004; Harmon-Jones et al. 2010). In a randomized sham-controlled crossover design, participants performed the EMOBACK task at baseline and after low-frequency stimulation of the left or right DLPFC in two subsequent sessions.

In a third study, we extended the investigation of neural correlates of emotional working memory by additionally considering state-dependent effects of rTMS. The importance of this experimental approach arises from a growing body of research demonstrating that the preactivation of the targeted cortical region can strongly influence stimulation effects (for a review, see Silvanto et al. 2008). We used tDCS in order to modulate the neural activation state prior to low-frequency rTMS applied over the right DLPFC. Each participant received anodal and cathodal tDCS followed by either active or sham rTMS before performing the EMOBACK task.

In addition, this thesis aimed at investigating the effects of OXT on emotion memory processing. Conflicting findings of previous research demonstrated both memory-enhancing (Guastella et al. 2008; Rimmele et al. 2009; Savaskan et al. 2008) and memory-impairing oxytocinergic effects (Herzmann et al. 2012). In a double-blind placebo-controlled design, we explored the influence of a single (prior to encoding) and a repeated (prior to encoding and retrieval) intranasal administration of OXT on recognition memory for emotional stimuli taken from the International Affective Picture System (IAPS; Lang et al. 2008). Furthermore, we assessed the interaction of emotion regulation processes and OXT-induced memory effects.

2 Neural Mechanisms underlying the Integration of Emotion and Working Memory

Grimm S* & Weigand A*, Kazzer P, Jacobs AM, Bajbouj M (2012). Neuroimage 61:1188-1194

http://dx.doi.org/10.1016/j.neuroimage.2012.04.004

2.1 Abstract

The present study aimed at investigating the behavioral effects and neuronal correlates of emotional content and emotional components, i.e. valence and arousal, in the context of a verbal working memory task. Our findings in twenty healthy male subjects demonstrate that (1) word valence has no impact on performance in the verbal working memory task, and (2) that emotion leads to an increase of activation in cognition-related lateral prefrontal regions, whereas cognitive effort yields enhanced deactivation in emotion- related cortical midline regions. The stronger dorsolateral prefrontal recruitment during emotional stimuli may reflect an arousal effect or higher cognitive effort due to interference with emotion.

2.2 Introduction

There are numerous experiences in our everyday life showing that information and situations associated with emotions are better remembered. While an emotional enhancement effect on episodic memory performance has been shown in several studies at the behavioral as well as at the neural level (Buchanan and Adolphs 2003; Kensinger and Corkin 2003; Smith et al. 2005), less is known about the relation between emotion and working memory (WM).

WM is an essential component of many cognitive operations, from complex decision making to selective attention (Baddeley 1986). One commonly utilized WM task is the

n-back task, which requires participants to monitor series of stimuli and to respond whenever a stimulus is presented that is the same as the one presented n trials previously. The task requires subjects to continually adjust the information held in working memory, to incorporate the most recently presented stimulus while simultaneously rejecting or ignoring more temporally distant stimuli. N-back tasks have been used to demonstrate that the dorsolateral prefrontal cortex (DLPFC) is implicated in numerous cognitive functions relevant to WM, including holding to-be-remembered information on-line (Goldman-Rakic 1994; Jonides et al. 1993), monitoring and manipulating the to-be-remembered information (Petrides 1994), response selection (Rowe et al. 2000), and implementation of strategies to facilitate memory (Bor et al. 2003; 2004). Activity in the anterior cingulate cortex (ACC) during n-back tasks is often described in relation to increased effort, complexity, or attention (Duncan and Owen 2000; Botvinick et al. 2004). While the exact role of the ACC is still debated, most theories suggest a role in cognitive control, including error detection, conflict monitoring, and/or task switching (Botvinick et al. 2004; Carter and van Veen 2007; Hyafil et al. 2009).

Previous emotion and WM research has found that while emotional state, mood, or context influences working memory (Gray et al. 2002; Erk et al. 2007; Aoki et al. 2011), the use of emotional stimuli has no consistent impact on working memory performance. For example, Kensinger and Corkin (2003) examined how the emotional content of stimuli influenced working memory performance across different tasks. They found no influence of emotion on accuracy, but slower reaction times for negative compared to neutral stimuli in a nonverbal working memory task. A recent study by Becerril and Barch (2011) supports these findings to some extent by showing higher accuracy but slower reaction times for negative compared to neutral nonverbal stimuli. Other studies using emotional stimuli reported no impact whatsoever on WM performance (Perlstein et al. 2002; Döhnel et al. 2008). Regarding the question whether emotional content affects processes supporting working memory, Perlstein et al. (2002) found evidence that emotional content reduced working memory related brain activation in right DLPFC. This result would suggest that emotional content might hinder performance on working memory tasks. Two recent fMRI studies however reported either no effect of emotional content on DLPFC activity (Döhnel et al. 2008) or increased DLPFC activity during an emotional WM task (Neta and Whalen 2011).

It is also still unclear how working memory performance and associated brain activation is mediated by the properties of an emotional stimulus. One dimensional approach to emotion emphasizes the contribution of two orthogonal components, namely arousal and valence (Lang et al. 1999; Russell 1980). Arousal refers to how strongly an emotion is experienced on a continuum that varies from calm to excitement. Valence refers to the subjective experience of the affective value or quality of an emotional stimulus independent of its sensory quality on a continuum that varies from positive to negative with neutral in the middle (Bradley and Lang 1994). Imaging studies demonstrated that arousal and valence differ not only psychologically, but also in their neural substrates (Anderson et al. 2003; Dolcos et al. 2004; Grimm et al. 2006; Viinikainen et al. 2010). Arousal has been linked to neural activity in the amygdala as well as in the dorsomedial prefrontal cortex (DMPFC) (Anders et al. 2004; Dolcos et al. 2004; Grimm et al. 2006). Valence has been associated with neural activity in medial prefrontal cortex (ventromedial prefrontal cortex and pregenual anterior cingulate; VMPFC/ PACC) and lateral prefrontal cortex including ventrolateral (VLPFC) and dorsolateral (DLPFC) prefrontal cortex (Dolcos et al. 2004; Grimm et al. 2006). The valence hypothesis states that the left prefrontal cortex is dominant in the processing of positive emotions, whereas the right prefrontal cortex is dominant in the processing of negative emotions (Davidson and Irwin 1999). There is some evidence for valence related specificity in medial prefrontal cortex (George et al. 1995; Paradiso et al. 1999) during approach or appetitive tasks, supporting the role of this region in appetitive or reward circuits (Rolls 2000; Wager et al. 2003). On the other hand numerous studies described medial prefrontal involvement in processing emotionally stimuli irrespective of valence (for a review, see Phan et al. 2002), therefore suggesting that its involvement could be attributed to its role in the processing of arousal. Only few studies have investigated the effects of valence and arousal on working memory performance using fMRI and reported conflicting results: While Perlstein at al. (2002) found reduced activation in right DLPFC during negative stimuli, Döhnel et al. (2008) report no valence- or arousal specific effects in prefrontal cortex. Conversely, Becerril and Barch (2011) used a nonverbal *2*-back task and found greater activation in left DLPFC during negative and in the medial prefrontal cortex during positive stimuli. All these studies used nonverbal stimuli to investigate the effect of emotional content on WM performance and associated neural activity which raises the question how the

interaction between emotional content, WM performance and associated neural activity might be influenced during a verbal WM task. Previous studies found domain related specificity with increased left prefrontal activity during verbal and increased right prefrontal activity during non- verbal WM tasks (Smith et al 1996; Smith and Jonides 1999).

The aim of the present study was to investigate the behavioral and neural effects of emotional content and emotional components, i.e. valence and arousal, in the context of a verbal working memory task. We employed a 2-back task with standardized emotional words from the Berlin Affective Word List (BAWL; Võ et al. 2009) and incorporated positive, negative and neutral words matched according to different arousal levels in order to elucidate valence and arousal effects. The experiment was conducted with respect to the following questions: (i) Is verbal working memory influenced by emotion and is this effect valence- or arousal dependent? (ii) How does the integration of emotion and WM processes affect brain activity in emotion- related (medial PFC) and WM- related (DLPFC) regions? (iii) Is WM associated brain activity differentially dependent on arousal or valence? (iv) Are there any lateralization effects due to domain and/ or valence specificity?

2.3 Methods

2.3.1 Subjects

Twenty healthy male subjects (age 23.5 ± 2.4; range 18- 28 years; IQ 106.7 ± 6.7) were recruited through advertisements. Somatic as well as psychiatric health status was evaluated by a structured psychiatric interview (Mini-International Neuro-psychiatric Interview; Sheehan et al. 1998) performed by a psychologist. No subject had to be excluded due to fulfilling the criteria for an axis I or axis II disorder according to DSM-IV criteria, diagnosed neurological and general medical disorders or clinically relevant abnormalities. Mood and arousal before and after the experiment were measured by means of the Multidimensional Mood Questionnaire (MDBF; Steyer et al. 1997). Intelligence was assessed using a word recognition test (WST; Schmidt and Metzler 1992), which is functionally equivalent to the widely used NART

test (Nelson and O'Connell 1978). All subjects were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield 1971). The study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the Institutional Review Board of the Charité University Medicine (Berlin, Germany). All subjects gave written informed consent before screening.

2.3.2 Experimental Design

Emotional stimuli were German nouns taken from the Berlin Affective Word List (BAWL, Võ et al. 2009). According to the BAWL norms, the emotional words were classified as positive, negative and neutral (35 different words per condition). The words of the three valence conditions were matched for word length (5-8 letters), imageability and frequency (total frequency of appearance per million words). The emotional arousal was equivalent in the positive and negative condition. The stimuli were consecutively presented within a 2-back working memory task (Fig. 7), which provides a novel means of studying the interface between verbal working memory and emotion. Subjects were required to monitor a series of words and to respond whenever a word was presented that was the same as the one presented 2 trials previously. Subjects performed a practice run prior to the experiment followed by 15 blocks of experimental trials. Each block consisted of 15 words of either positive, negative or neutral valence presented for 500ms with an interstimulus interval (ISI) of 1500 ms and was followed by a fixation trial (10-14 sec). During the experiment 75 words per condition were presented. The condition order was randomized across the task. Stimuli were generated by Presentation® (Neurobehavioral Systems, Inc., Albany, CA, USA) and presented via video goggles (VisuaStim digital). Participants responded by pushing a fiber-optic light sensitive key press.

After the fMRI session participants rated all emotional words presented during the task on a 7-point scale regarding emotional valence (-1=very negative/ 3=very positive) and on a 5-point scale regarding emotional arousal (1=not arousing/ 5=very arousing) according to the BAWL norms.

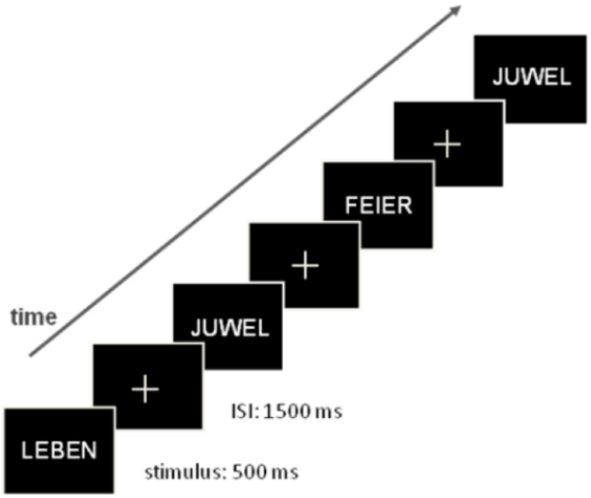

Fig. 7. Experimental Paradigm. Schematic representation of the n-back task. Word stimuli of either positive, negative or neutral valence presented for 500ms with an interstimulus interval (ISI) of 1500 ms and followed by a fixation trial (10-14 sec).

2.3.3 Functional Imaging

Functional data were acquired on a Siemens Trio 3T scanner using a standard echo planar imaging sequence with 37 oblique axial slices of 3 mm (field of view 192 mm, 3 x 3 mm in- plane, repetition time 2 s, echo time 30 ms, flip angle 70°). One run of 331 volumes was acquired, as well as a T1- weighted high-resolution MP-Rage scan.

2.3.4 Statistical analysis

Behavioral data:

Accuracy was defined as the ratio of correct responses (correctly pressed and correctly not pressed) to total number of stimuli. Reaction times of the correct responses were analyzed. Accuracy and reaction times were analyzed using a one-way analysis of variance (ANOVA) for the factor valence (positive, negative, neutral). In the same manner, the valence and arousal word ratings were analyzed. Further

statistical analysis was done using post hoc t-tests. All tests were two-tailed and the significant threshold was set at a probability of $p<0.05$. All statistical analyses were carried out using PASW (version 18.0, Chicago: SPSS Inc., Illinois, USA).

FMRI data:

FMRI data were analyzed using MATLAB 2008b (The Mathworks Inc., Natick, MA, USA) and SPM8 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). Functional data were realigned to the first volume, corrected for motion artefacts, mean-adjusted by proportional scaling, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute), and spatially smoothed using a 6 mm FWHM Gaussian kernel. The time series were high-pass filtered to eliminate low-frequency components (filter width 128 s) and adjusted for systematic differences across trials. Statistical analysis was performed by modeling the different conditions convolved with a hemodynamic response function as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. Realignment parameters were included as additional regressors in the statistical model. A fixed-effect model at a single-subject level was performed to create images of parameter estimates, which were then entered into a second-level random-effects analysis. For the fMRI data group analysis the contrast images from the analysis of the individual participants were analyzed using one-sample t tests. Clusters of activation were identified with a global height threshold of $p < 0.001$, uncorrected and a cluster threshold of greater than 25. FMRI analyses focused on the effect of emotion on the n-back task. Then ROI analyses were performed to further investigate signal changes and to correlate them with measures for valence and arousal. For the ROI analyses of peak voxels, coordinates which were obtained in the group analyses (Table 1) were selected. Regions of interest were functionally defined by centering spheres on the respective peak voxels with a radius of 5 mm. Analyses were carried out for the left dorsolateral prefrontal cortex (lDLPFC; -36, 5, 38), right dorsolateral prefrontal cortex (rDLPFC; 42, 41, 34), dorsal anterior cingulate cortex (dACC; 9, 23, 37), rostral anterior cingulate cortex (rACC; -3, 29, -5), pregenual anterior cingulate cortex/ ventromedial prefrontal cortex (PACC/ VMPFC; 6, 59, 4), dorsomedial prefrontal cortex (DMPFC; 0, 53, 37) and posterior cingulate cortex (PCC; 3, -46, 31). For the ROI analyses, % signal changes for the different conditions were extracted

for each subject separately using Marsbar (http://marsbar.sourceforge.net). For each event % signal changes were calculated relative to the mean signal intensity of this ROI across the whole experiment. To detect the association of signal changes in response to the emotional component of the n-back task with postscanning ratings of valence and arousal, the correlation between the individual scores of postscanning ratings and signal changes in the regions of interest was analyzed in a post- hoc, region- of- interest analysis using Marsbar (see above). Subjects' individual scores were correlated with signal changes during emotional words using Pearson correlation analysis.

2.4 Results

2.4.1 Behavioral Results

Reaction Times:

There was a trend for slower reaction times in negative compared to positive words [negative words: 474.98 ms ± 103.6; positive words: 440.35 ms ± 90.0 (mean ± SD); $t(1,19) = 2.07$, $p = 0.05$].

Accuracy:

No significant effect of word valence on accuracy measures for positive, negative and neutral words was obtained.

Postscanning Ratings:

ANOVAs showed a significant main effect of valence for both the emotional valence and arousal ratings [valence: $F(2,38) = 102.88$, $p<0.001$; arousal: $F(2,38) = 23.05$, $p<0.001$]. Post hoc comparisons revealed that valence ratings systematically varied with emotion condition: positive words were rated significantly more pleasant than negative [$t(1,19) = 10.74$, $p<0.001$] and neutral words [$t(1,13) = 11.63$, $p<0.001$]. Neutral words were rated significantly more pleasant than negative words [$t(1,13) = 8.05$, $p<0.001$]. Regarding the emotional arousal ratings, neutral words were rated significantly less arousing than negative [$t(1,13) = 4.00$, $p<0.001$] and positive words

[t(1,13) = 7.07, p<0.001]. Furthermore, positive words were rated significantly more arousing than negative [t(1,19) = 2.39, p<0.05].

2.4.2 FMRI Results

To investigate how the integration of emotion and WM processes affect brain activity in emotion- related and WM- related regions, the first step of the analysis focused on the effects of emotional and neutral words in the context of a 2-back task. Task conditions were associated with BOLD signal changes in bilateral DLPFC, dACC, medial cortical regions such as VMPFC/PACC, DMPFC, PCC, medial temporal gyrus and also in rostral ACC and orbitofrontal cortex. We then performed ROI analyses to ascertain whether signal increases or decreases were associated with positive, negative and neutral words in the respective regions. These analyses revealed that the *2*-back task induced activations (signal increases) in bilateral DLPFC and dACC, but deactivations (signal decreases) in cortical midline regions such as PACC/ VMPFC, DMPFC, PCC and rostral ACC. Emotional words yielded higher signal increases than neutral words in bilateral DLPFC, while cortical midline regions showed higher signal decreases during neutral words. Bar diagrams show clear differential involvement of DLPFC and cortical midline regions in emotional and neutral words during the working memory task (see Table 1 and Figures 8a and b).

Tab. 1. Effect of task conditions.

Region	Emotional vs. Neutral Words	Positive vs. Negative Words
Right DLPFC	42 41 34 z: 4.29	
Left DLPFC	-36 5 38 z: 4.71	
rACC	-3 29 -5 z: 5.22	
PACC/ VMPFC	6 59 4 z: 6.37	
dACC	9 23 37 z: 4.10	9 23 37 z: 5.85
DMPFC	0 53 37 z: 5.05	
OFC	-30 32 -14 z: 5.13	
PCC	3 -46 31 z: 4.86	
Right Insula	33 23 7 z: 4.72	30 20 -8 z: 3.79
Left Insula	-27 20 7 z: 5.95	
Left MTG	-54 2 -23 z: 5.29	
Right MTG	60 -4 -23 z: 5.44	
Right Putamen	18 11 7 z: 3.77	
Left Putamen	-18 5 10 z: 4.27	
Right Thalamus	12 -4 4 z: 3.76	9 -1 7 z: 4.75
Right Parietal Cortex	39 -46 43 z: 4.70	
Left Parietal Cortex	-30 -49 43 z: 5.76	
Right Occipital Cortex	36 -91 -5 z: 4.99	
Left Occipital Cortex	-24 -100 -2 z: 5.51	
Left Premotor Cortex	-6 14 46 z: 5.69	

DLPFC Dorsolateral Prefrontal Cortex, rACC Rostral Anterior Cingulate Cortex, PACC Pregenual Anterior Cingulate Cortex, VMPFC Ventromedial Prefrontal Cortex, dACC Dorsal Anterior Cingulate Cortex, DMPFC Dorsomedial Prefrontal Cortex, OFC Orbitofrontal Cortex, PCC Posterior Cingulate Cortex, MTG Medial Temporal Gyrus. The global height threshold was set to $p < 0.001$ uncorrected, the extent threshold to $k = 25$ voxels for all contrasts. The values in the table represent maximum z values with peak voxel coordinates in the MNI stereotactic space.

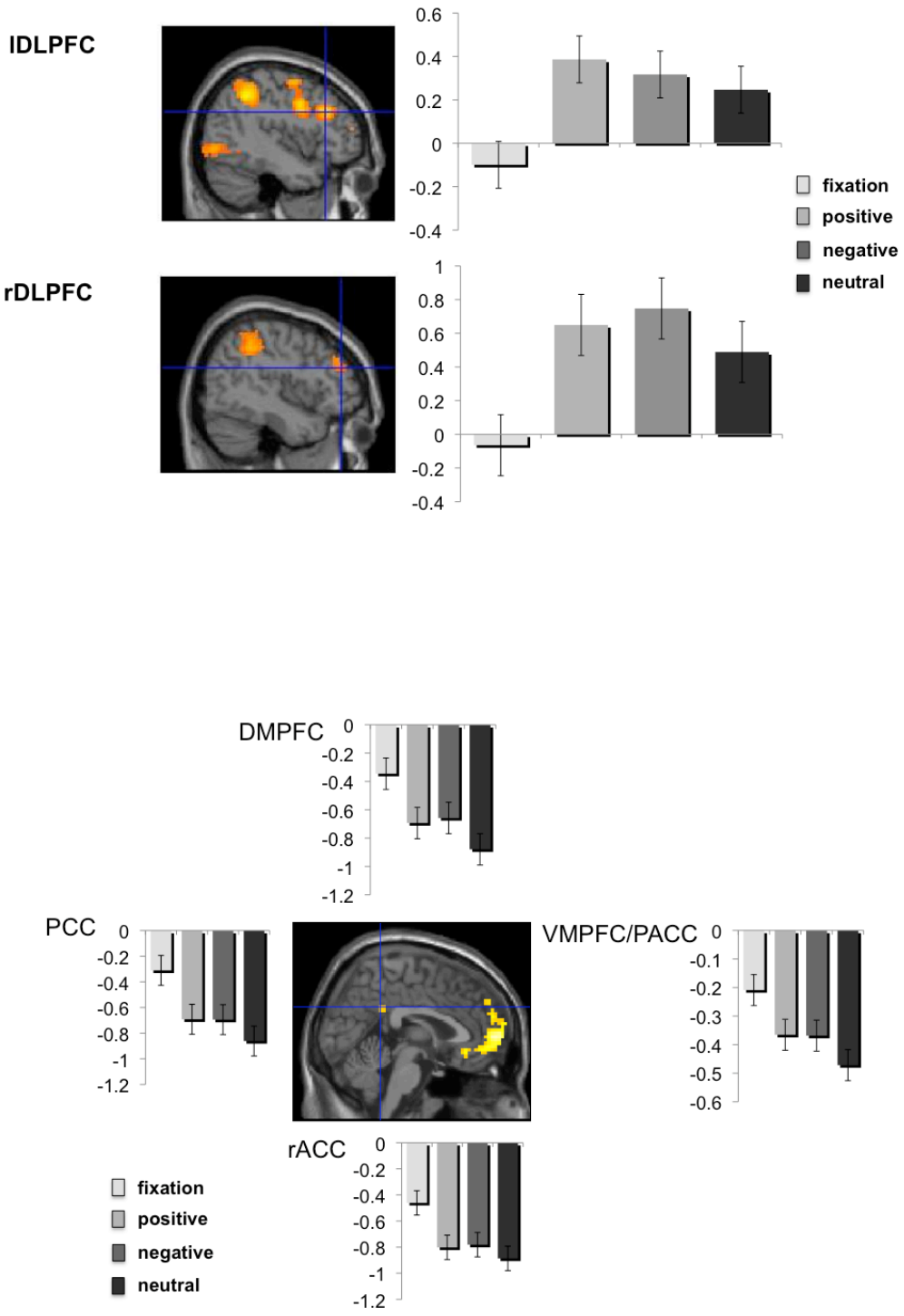

Fig. 8. a and b. Effect of emotional and neutral words. Signal changes during fixation cross, positive, negative and neutral words in (a) bilateral DLPFC [left DLPFC (-36, 5, 38) and right DLPFC (42, 41, 34)] and (b) cortical midline regions [PCC (3, -46, 31), DMPFC (0, 53, 37), VMPFC/ PACC (6, 59, 4) and rACC (-3, 29, -5)].

The conditions positive words vs. negative words were contrasted to obtain signal changes specific for each valence. The comparison negative > positive (N > P) revealed significantly higher signal intensities in dACC, right insula and right thalamus (see Table 1 and Figure 9). No significant differential activations were found for the opposite contrast P > N.

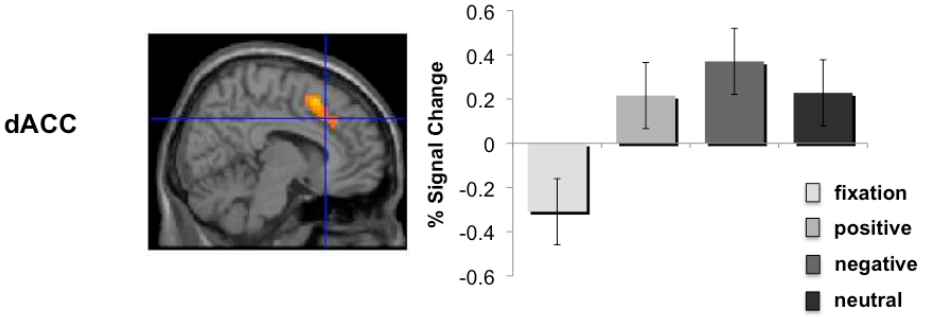

Fig. 9. Effect of Emotional Valence. Signal changes during fixation cross, positive, negative and neutral words in the dACC (9, 23, 37).

Parametric dependence of neural activity on emotional valence and arousal was investigated by correlating postscanning ratings of positive, negative and neutral words with fMRI signal changes during the working memory task for emotional words. Signal changes in right DLPFC correlated with arousal ratings regardless of valence (positive words: $r= 0.67$, $p < 0.001$; negative words: $r= 0.55$, $p < 0.05$; neutral words: $r= 0.50$, $p < 0.05$). Signal changes in VMPFC correlated with valence ratings for positive words ($r= 0.57$, $p < 0.05$).

No relationship between signal changes during the n-back task and accuracy of task performance was obtained. Reaction times for positive words correlated with signal changes in left DLPFC ($r= 0.48$, $p < 0.05$).

In an exploratory analysis we investigated differences between subjects classified as „high emotional“ or „low emotional“ according to their posthoc valence ratings. Subjects were classified as „high emotional“ if they rated positive and negative words very high or low, respectively. „High emotional“ subjects showed significantly higher signal intensities in left DLPFC during the n-back task for positive words ($p < 0.05$) and in the dACC during the n-back task for negative words ($p < 0.05$).

2.5 Discussion

Our findings demonstrate that emotional content has no impact on performance in a verbal working memory task. It is interesting to note though, that while reaction times for emotional and neutral stimuli did not differ significantly during the n-back task, reaction times in positive stimuli were numerically faster and indicate a stronger arousal effect of positive compared to negative and neutral words. This is also supported by results of the postscanning ratings, which confirmed that positive words were experienced as significantly more arousing. Results also revealed differential involvement of prefrontal cortex in the emotional working memory task. While emotion leads to an increase of activation in cognition- related lateral prefrontal regions, cognitive effort yields enhanced deactivation in emotion- related cortical midline regions. Although there were no valence- specific effects in DLPFC, negative words elicited stronger signal increases in dACC. During the emotional WM task neural activity was modulated in right DLPFC by arousal and in VMPFC by positive valence. Furthermore, slower reaction times for positive words were correlated with neural activity in left DLPFC.

Our findings regarding WM performance are in accordance with previous studies that found no impact of emotion on working memory performance (Perlstein et al. 2002; Döhnel et al. 2008). Even though not statistically significant, our finding of slower reaction times in negative words confirms results by Kensinger and Corkin (2003) and Becerril and Barch (2011) who reported slower reaction times for negative stimuli in a nonverbal WM task. One could hypothesize that reaction times may be more sensitive to small modulations by emotional content than is accuracy and therefore emotional content may be more likely to modulate the efficiency with which information is processed as compared with the accuracy with which it is held online. The recruitment of neural networks implicated in emotion processing might result in additional inputs to the working memory system (e.g., those associated with emotion and arousal; LeDoux 2002). Therefore, it may be that many additional facets of information must be inhibited to allow for processing of only the task-relevant information in the context of the 2-back task. This increased demand on inhibition may slow the response times. The emotional content increased WM related brain activation in bilateral DLPFC, as mentioned above, this did not result in improved WM

performance during emotional stimuli, though. N-back tasks have been used in numerous studies to demonstrate that the DLPFC is implicated in WM (Goldman-Rakic 1994; Jonides et al. 1993; Petrides 1994; Rowe et al. 2000; Bor et al. 2004), but it has been suggested that emotional content reduces working memory related brain activation in right DLPFC and might therefore hinder performance (Perlstein et al. 2002). In our study, emotional content did neither impair nor improve the performance in the WM task, but elicited more neural recruitment in bilateral DLPFC, which might reflect that more DLPFC activity is necessary to maintain performance despite emotional stimuli (Neta and Whalen 2011). The finding that neural responses during WM are associated with reaction times supports this: the more DLPFC recruitment during emotional words, the longer the reaction times. As also suggested by the behavioral results, reaction times as a more sensitive indicator of task performance show that more activity in DLPFC is necessary to perform the WM task (Neta and Whalen 2011).

In contrast to previous studies we used verbal stimuli to investigate the effect of emotional content on WM performance and associated neural activity, which might explain the conflicting findings. Furthermore, Perlstein et al. (2002) who reported reduced activation in rDLPFC during emotional WM used a modified delayed match-to-sample task, which might not be associated with the same neural activity pattern as a n-back task. Indeed, two previous studies which employed a n-back task with nonverbal emotional stimuli reported either no effect of emotional content on DLPFC activity (Döhnel et al. 2008) or increased DLPFC activity (Neta and Whalen 2011).

The higher overall signal intensities in right than in left DLPFC in our study indicates stronger recruitment of right DLPFC in the WM task, which confirms findings by Erk et al. (2007). An explanation might be, that even though a verbal task would require less right DLPFC engagement due to domain related specificity with increased left prefrontal activity during verbal and increased right prefrontal activity during non-verbal WM tasks (Smith et al. 1996; Smith and Jonides 1999), the right DLPFC is additionally recruited in an implicit emotional judgement task (Northoff et al. 2004; Grimm et al. 2008).

We failed to see any general lateralization pattern of valence- related activity. Even though there was a stronger recruitment of left DLPFC during positive and right DLPFC during negative words, the difference was not statistically significant. The

inclusion of neutral words allowed us to disentangle valence from arousal effects. Both valence conditions boosted a signal gain in DLPFC, which may result from an arousal effect or reflect higher cognitive effort due to interference with emotion. The hypothesis of a general arousal effect is supported by the association of left DLPFC signal intensities with arousal, but not with valence ratings as well as by results in high emotional subjects. The correlation between left DLPFC activity and longer reaction times for positive words suggests a subtle specific effect as stated in the valence hypothesis with dominant processing of positive emotions in the left prefrontal cortex (Davidson and Irwin 1999). Stronger recruitment of left DLPFC during the emotional component of the task may result in affected performance in the cognitive task as reflected in longer reaction times. Imaging studies linked arousal to neural activity in the amygdala as well as in the dorsomedial prefrontal cortex (DMPFC) (Anders et al. 2004; Dolcos et al. 2004; Grimm et al. 2006), while valence has been associated with neural activity in medial prefrontal cortex (ventromedial prefronal cortex and pregenual anterior cingulate; VMPFC/ PACC) and lateral prefrontal cortex including ventrolateral (VLPFC) and dorsolateral (DLPFC) prefrontal cortex (Dolcos et al. 2004; Grimm et al. 2006). The difference to our findings might be due to the fact that our task was not “purely” emotional but rather a cognitive task with emotional confounds. A significant effect of negative emotional valence was found in dACC, an effect earlier described by Viinikainen et al. (2010). Activity in this region during n-back tasks is often described in relation to increased effort, complexity, or attention (Duncan and Owen 2000; Botvinick et al. 2004). Since negative words seem to be less arousing in the context of a n-back task (see behavioral results) the distinction between cognitive and emotional processing might be less defined and they therefore elicit more neural activity in dACC due to increased conflict monitoring, and/or task switching (Botvinick et al. 2004; Carter and van Veen 2007; Hyafil et al. 2009). This is also supported by the significantly higher dACC activation during negative words. The lower activity in dACC during neutral stimuli might be associated to decreased conflict between cognitive and emotional task components. In cortical midline regions such as VMPFC/PACC, DMPFC, rACC and PCC we found a stronger effect of neutral words as compared to emotional words: cognitive effort without emotional confounds (neutral stimuli) leads to stronger deactivation in emotion- related brain regions. These cortical midline regions are part of the default-mode network (Raichle et al. 2001; Raichle and Gusnard 2005) and

characterized by deactivations during various emotional– cognitive tasks that require subjects to attend to external stimuli (Gusnard et al. 2001; Northoff et al. 2004; Raichle and Gusnard 2005; Grimm et al. 2009). The converse relationship between medial and lateral prefrontal activity during emotional- cognitive interaction has been described as reciprocal modulation (Northoff et al. 2004) and stronger anticorrelations between these areas have been associated with better working memory performance (Hampson et al. 2010).

We found that only the neural activity in VMPFC during the emotional WM task was parametrically modulated by positive valence. Valence has previously been associated with neural activity in VMPFC (Dolcos et al. 2004; Grimm et al. 2006; Wager et al. 2003; Viinikainen et al. 2010). On the other hand numerous studies described medial prefrontal involvement in processing emotionally stimuli irrespective of valence (for a review, see Phan et al. 2002; Viinikainen et al. 2010; Colibazzi et al. 2010), therefore suggesting that its involvement could be attributed to its role in the processing of arousal, which is supported by the results in the other cortical midline regions where we found neither differential valence- dependent activity nor a parametric modulation of activity by valence.

There are several limitations to this study. The rather small sample size of this investigation has to be considered when interpreting the results. We only included a 2-back task and did not test the effects of increasing cognitive load. While load is often varied up to 3-back (Owen et al. 2005; Neta and Whalen 2011), some authors have questioned the validity of results when the ability to successfully perform the task decreases (Callicott et al. 1999). Nevertheless, we cannot exclude the possibility that findings might be confounded due to a ceiling effect. Furthermore, we confined the study to males within a limited age range. Gender differences have previously been observed in emotion paradigms (Wrase et al. 2003; Sabatinelli et al. 2004). These studies investigated the effect of affective pictures without a cognitive task, while we focused on a cognitive task with emotional content. To rule out a gender specific effect subsequent studies should include female subjects.

2.6 Conclusion

The current study indicates that emotional content has no impact on performance in a verbal WM task. Regions of the prefrontal cortex are differentially involved in the emotional working memory task. Emotion leads to an increase of activation in cognition- related lateral prefrontal regions, cognitive effort yields enhanced deactivation in emotion- related cortical midline regions. The stronger DLPFC recruitment during emotional stimuli could reflect an arousal effect or higher cognitive effort due to interference with emotion. The hypothesis of a general arousal effect is supported by the parametric modulation of DLPFC activity by arousal, while no valence- specific effects could be observed. Deactivations in cortical midline regions were stronger during neutral stimuli and parametrically modulated by valence.

3 Lateralized Effects of Prefrontal Repetitive Transcranial Magnetic Stimulation on Emotional Working Memory

Weigand A, Grimm S, Astalosch A, Guo JS, Briesemeister BB, Lisanby SH, Luber B, Bajbouj M (2013). Experimental Brain Research 227(1):43-52

http://dx.doi.org/10.1007/s00221-013-3483-7

4 State-dependent Effects of Prefrontal Repetitive Transcranial Magnetic Stimulation on Emotional Working Memory

Weigand A* & Richtermeier A*, Feeser M, Guo JS, Grimm S, Bajbouj M. (2013). Brain Stimulation, Epub ahead of print

http://dx.doi.org/10.1016/j.brs.2013.06.004

4.1 Abstract

A growing body of findings illustrates the importance of state-dependency in studies using brain stimulation. We aimed to investigate the effects of tDCS priming followed by rTMS applied over the right DLPFC on emotional working memory. In a randomized single-blind within-subjects design, participants performed an emotional 3-back task at baseline and after tDCS priming (anodal, cathodal) and subsequent low-frequency rTMS (active, sham) of the right DLPFC. Stimuli consisted of words related to the distinct emotion categories fear and anger as well as neutral words. Task accuracy increased for fear-related words and decreased for neutral words across stimulation conditions. No general state-dependent effects of prefrontal rTMS on working memory were found. We further showed a detrimental effect of negative emotional content on working memory performance. Our findings support a hemispheric lateralization of emotion processing by demonstrating that the withdrawal-related emotion fear is associated with the right DLPFC and contribute to clarifying the interaction between working memory and emotion.

4.2 Introduction

Growing evidence indicates that effects of brain stimulation strongly depend on the level of neuronal activity at the time of stimulation (for a review, see Silvanto et al. 2008). However, most studies take no account of the initial state in the stimulated brain region. It has been argued that this lack of control is likely to be one of the key

factors explaining inconsistencies in reported stimulation effects, including clinical treatment trials (Lang et al. 2004; Langguth et al. 2008). State-dependent effects of repetitive transcranial magnetic stimulation (rTMS) have extensively been explored in the motor cortex by measuring motor-evoked potentials (MEP) (Siebner et al. 2009). Interestingly, it has been demonstrated that priming with transcranial direct current stimulation (tDCS) reversed the expected effects of low-frequency rTMS applied to the primary motor hand area (M1): While excitatory anodal tDCS followed by 1 Hz rTMS resulted in reduced cortical excitability, inhibitory cathodal tDCS followed by 1 Hz rTMS produced increased cortical excitability (Siebner et al. 2004). Similar converse changes in MEP amplitudes after tDCS priming were found for subsequent high-frequency rTMS (Cosentino et al. 2012; Lang et al. 2004). Further experimental data from the motor cortex demonstrated that high-frequency rTMS can also be used as a priming tool, enhancing the suppressive effect of subsequent low-frequency rTMS (Iyer et al. 2003). In agreement with these findings derived from motor cortex physiology, clinical evidence revealed that preceding high-frequency rTMS improves the efficacy of low-frequency rTMS applied to the right dorsolateral prefrontal cortex (DLPFC) in the treatment of depression (Fitzgerald et al. 2008; Nongpiur et al. 2011). Cathodal tDCS priming followed by high-frequency rTMS applied to the left DLPFC did not result in greater antidepressant effects, although one patient responded with a highly improved clinical outcome (Loo et al. 2010). The importance of state-dependent stimulation effects has additionally been illustrated in perceptual and cognitive studies investigating causal brain-behavior relationships. For example, by using adaptation to manipulate neural activation states prior to the application of TMS, specific and even spatially overlapping neuronal representations were examined when processing numbers (Kadosh et al. 2010) and words (Cattaneo et al. 2010a) as well as during visual motion perception (Cattaneo et al. 2010b).

Based on these considerations, the primary aim of our study was to assess the effects of tDCS priming followed by rTMS applied over the DLPFC in healthy participants on the performance in an emotional working memory task.

Working memory refers to the temporary storage and manipulation of information that is no longer accessible in the environment (D'Esposito et al. 2000; Goldman-Rakic 1995). Numerous neuroimaging findings demonstrated a key role of the DLPFC in working memory processing (e.g. Braver et al. 2001; Curtis and D'Esposito 2003;

Jonides et al. 1997), supported by studies using rTMS (Hamidi et al. 2009; Luber et al. 2007; Mottaghy et al. 2000; Sandrini et al. 2008) and tDCS (Fregni et al. 2005; Mulquiney et al. 2011; Ohn et al. 2008; Sandrini et al. 2012; Zaehle et al. 2011). The interaction of working memory and emotion has been investigated only in a small number of studies, providing conflicting results. At the behavioral level, negative stimuli have shown both impairing (Kensinger and Corkin 2003; Lindström and Bohlin 2012; Perlstein et al. 2002) and facilitating (Lindström and Bohlin 2011) effects on task performance. Other studies found no behavioral impact of emotional content on working memory (Döhnel et al. 2008; Grimm et al. 2012). At the neuronal level, no consistent relationship was found between DLPFC activity and emotional stimuli (Döhnel et al. 2008; Grimm et al. 2012; Neta and Whalen 2011; Perlstein et al. 2002). Our own data (Grimm et al. 2012) have demonstrated a stronger recruitment of the right DLPFC while processing negative stimuli in working memory, supporting a valence-specific hemispheric lateralization in emotion processing (Davidson and Irwin 1999; Herrington et al. 2010). Furthermore, in our previous rTMS study (Weigand et al. 2013), we extended our neuroimaging findings by demonstrating a causal role of the right DLPFC in working memory for negative, withdrawal-related words. These findings provided further support for the motivational direction model, which states that the right prefrontal cortex is dominant in the processing of withdrawal-related emotions, whereas the left prefrontal cortex is dominant in the processing of approach-related emotions (Harmon-Jones 2004; Harmon-Jones et al. 2010). In line with this model, the left prefrontal cortex has been found to process anger, a negatively valenced emotion that is associated with approach motivation (Harmon-Jones 2003).

Therefore, the second aim of our study was to further explore our previous findings of prefrontal hemispheric lateralization in emotional working memory processing by distinguishing negative stimuli into withdrawal- and approach-related categories.

Participants were presented with an emotional n-back (EMOBACK) task consisting of words related to the distinct emotion categories fear and anger as well as neutral words. In a 2 (anodal, cathodal tDCS priming) x 2 (active, sham rTMS) randomized single-blind within-subjects design, task performance was measured at baseline and after combined tDCS priming (1 mA, 15 min) and subsequent rTMS (1 Hz, 15 min, 110% MT) of the right DLPFC.

Based on evidence of state-dependency of rTMS-induced changes (Cosentino et al. 2012; Fitzgerald et al. 2008; Iyer et al. 2003; Lang et al. 2004; Nongpiur et al. 2011; Siebner et al. 2004), we hypothesized that the direction of aftereffects produced by low-frequency rTMS depends on the polarity of tDCS priming. In accordance with the motivational direction model (Harmon-Jones 2004; Harmon-Jones et al. 2010), we expected that stimulation of the right DLPFC would especially influence task performance for fear-related words, which are associated with withdrawal motivation. Due to inconsistent findings of the impact of emotional content on working memory processing, no specific predictions were made about the direction of stimulation-induced changes in task performance.

4.3 Methods

4.3.1 Sample

Fifteen healthy volunteers (8 females) participated in the study (mean age 25.3 ± 4.0, range 19-32 years). All participants were right-handed (EHI; Oldfield 1971) native German speakers and naïve to rTMS. Their intelligence levels were at or above the range of norm (MWT-B; Lehrl 2005). No participants reported any previous or concomitant neurological or psychiatric condition (SCID; Wittchen et al. 1997) or any contradictions to rTMS (Rossi et al. 2009; Wassermann 1998). To exclude epileptiform activity, every participant underwent resting-state electroencephalography (EEG), screened by a trained physician. The study was approved by the Institutional Review Board of the Charité University Medicine (Berlin, Germany). All subjects gave their written informed consent in accordance with the ethical guidelines of the Declaration of Helsinki and were financially compensated for their participation.

4.3.2 Emotional working memory task

Based on our previous experiments (Grimm et al. 2012; Weigand et al. 2013), we used a verbal emotional n-back task (EMOBACK). Stimuli were German words taken from the Discrete Emotion Norms for Noun - Berlin Affective Word List (DENN-

BAWL; Briesemeister et al. 2011b). For the EMOBACK task, nouns strongly related to fear and anger were selected and controlled for valence and arousal (t's<1). In addition, neutral words were included in the task. The three emotion conditions were matched on imageability, number of letters, syllables, phonemes, frequency and orthographical neighbors (F's>1). Four parallel sets (Tab. 6), each consisting of 20 words per condition, were created with the described stimulus characteristics (t's<1).

Tab. 6. Stimulus characteristics used in the four parallel EMOBACK versions.

	Set 1			Set 2		
	Fear	Anger	Neutral	Fear	Anger	Neutral
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Valence	-1.2 (1.0)	-1.4 (0.8)	0.0 (0.2)	-1.2 (0.9)	-1.1 (0.9)	0.0 (0.2)
Arousal	3.6 (0.5)	3.5 (0.5)	2.4 (0.4)	3.6 (0.7)	3.4 (0.6)	2.5 (0.5)
Imageability	4.7 (1.4)	4.3 (1.1)	4.3 (1.5)	4.3 (1.3)	4.3 (1.0)	4.1 (1.3)
Letters	6.1 (1.2)	6.3 (1.5)	6.5 (1.1)	6.0 (1.1)	6.2 (1.5)	6.1 (1.1)
Syllables	2.0 (0.5)	2.1 (0.9)	2.2 (0.5)	1.9 (0.6)	2.0 (0.8)	2.1 (0.4)
Phonemes	5.5 (1.3)	5.6 (1.5)	5.3 (0.9)	5.3 (1.0)	5.3 (1.7)	5.4 (1.2)
Frequency	31.5 (45.5)	16.0 (23.5)	27.7 (51.8)	26.7 (43.8)	37.2 (56.1)	24.4 (42.2)
	Set 3			Set 4		
	Fear	Anger	Neutral	Fear	Anger	Neutral
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Valence	-1.3 (0.8)	-1.3 (0.9)	0.0 (0.3)	-1.2 (0.6)	-1.4 (0.7)	0.1 (0.3)
Arousal	3.6 (0.6)	3.4 (0.7)	2.4 (0.4)	3.5 (0.6)	3.5 (0.5)	2.3 (0.4)
Imageability	4.8 (1.2)	4.3 (1.0)	4.5 (1.4)	4.6 (1.4)	4.1 (1.3)	4.4 (1.1)
Letters	6.0 (1.3)	6.4 (1.2)	6.3 (1.0)	6.0 (1.3)	6.2 (1.3)	6.4 (1.2)
Syllables	2.1 (0.8)	2.2 (0.8)	2.2 (0.7)	2.0 (0.8)	2.0 (0.6)	2.1 (0.6)
Phonemes	5.4 (1.5)	5.8 (1.3)	5.4 (1.1)	5.5 (1.3)	5.5 (1.5)	5.6 (1.0)
Frequency	16.7 (23.8)	32.5 (69.2)	32.9 (46.8)	27.2 (83.2)	19.7 (42.5)	21.2 (31.2)

M Mean, SD standard deviation.

Words were presented in a randomized sequence within a 3-back task. Participants had to press a button whenever a presented word was the same as the one presented three trials earlier. A separate button indicated a non-target. Target and non-target button were located on opposite sides of a standard computer keyboard. Subjects were instructed to respond as quickly and as accurately as possible by using both index fingers. The words were presented for 500 ms in uppercase white letters centered on a black screen with an interstimulus interval (ISI) of 1500 ms. 18 words of the same emotion condition (fear, anger, neutral) were presented in a block, followed by a fixation period of 10 to 14 s. Participants were intensively trained in the task prior to the actual experiment. During task performance, they were seated 90cm in front of the monitor in a silent room and the monitor was placed at eye level. The EMOBACK task was programmed using Presentation® (Version 14.5, Neurobehavioral Systems Inc., San Francisco, CA, USA).

4.3.3 Experimental procedure

In a single-blind randomized within-subjects design, each participant underwent four different stimulation conditions: Anodal or cathodal tDCS priming followed by active or sham rTMS over the right DLPFC. Prior to the rTMS experiment, we acquired an anatomical high-resolution image for each participant on a Siemens Trio 3T scanner with conventional parameters (176 T_1-weighted images with a slice thickness of 1mm). The optimal stimulation site of the right DLPFC was marked individually using magnetic resonance imaging (MRI) non-stereotactic guidance (Peleman et al. 2010). In the first part of the experiment, two stimulation conditions were realized in successive sessions on the same day, separated by a 45-minute washout period to avoid carry-over effects (Bermpohl et al. 2005; Thut and Pascual-Leone 2010). Approximately a week later, the corresponding second part of the experiment was completed at the same time of day. In each stimulation condition, 15 randomized blocks of the EMOBACK task were presented at baseline and immediately after rTMS application (Figure 13). In total, 2160 stimuli (540 stimuli for each of the four stimulation conditions) were presented over the course of the experiment.

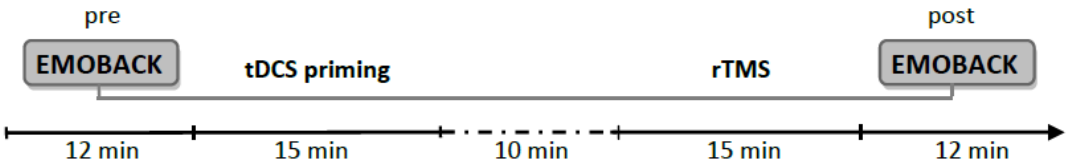

Fig. 13. Schematic illustration of the experimental design. Emotional n-back (EMOBACK) task performance was measured at baseline and after tDCS priming (anodal/cathodal) followed by low-frequency rTMS (active/sham) applied over the right DLPFC. A standardized time interval was implemented between subsequent stimulations.

4.3.4 tDCS priming

tDCS was delivered with a battery-driven constant current stimulator (CX-6650 DCS device by Rolf Schneider Electronics, Gleichen, Germany) using two electrodes placed in saline-soaked sponges (5 x 7 cm). Depending on the stimulation condition, either the anode or the cathode was placed on the right DLPFC. The reference electrode was placed on the left supraorbital area. tDCS was delivered for 15 min at 1 mA with a ramp time of 30 s.

4.3.5 rTMS

Biphasic magnetic stimulation was delivered with a Medtronic stimulator (MagPro X100, MagVenture, Farum, Denmark) connected to a figure-eight coil (MCF-B65) after a standardized time interval of 10 min (Siebner et al. 2004). In this period, an adjustable arm was adjusted to allow the precise coil position to be maintained throughout the experiment. The optimal stimulation site of the right DLPFC was marked individually using three-dimensional magnetic resonance imaging (3D-MRI) (Peleman et al. 2010). An anatomical high-resolution image was acquired for each participant on a Siemens Trio 3T scanner with conventional parameters (176 T_1-weighted images with a slice thickness of 1mm) approximately a week prior to the

actual experiment. The coil was angled at 45°, with the junction of the two coil wings placed perpendicular to the marked stimulation point on the skull using a neuronavigation system (eXimia Navigated Brain Stimulation (NBS), Nexstim, Helsinki, Finland). A placebo coil (MCF-P-B65) was positioned in the same manner for sham stimulation. rTMS was applied for 15 min at 1 Hz (900 pulses) with an intensity of 110 % of the resting motor threshold which was defined as the minimum intensity capable of evoking motor potentials of at least 50 μV recorded from the right first dorsal interosseus (FDI) in 5/10 stimulations.

4.3.6 Additional measures

To control for interindividual differences in characteristics that might influence task performance at baseline (Balconi and Mazza 2010; Bishop 2009; Harmon-Jones et al. 2010; Shackman et al. 2006; van Honk et al. 2001) or stimulation effects (Balconi and Ferrari 2012; Wassermann et al. 2001), we assessed the Big Five personality domains (NEO-FFI; Costa and McCrae 1992) as well as participants' predisposition to anxiety (STAI; Spielberger et al. 1983), anger (STAXI; Spielberger 1988) and approach and withdrawal behavior (ARES; Hartig and Moosbrugger 2003). Furthermore, subjects completed a mood questionnaire (MDBF: Steyer et al. 1997) prior to the EMOBACK baseline measurement (T_{pre}) and immediately after rTMS application (T_{post}). After each stimulation condition, valence and arousal ratings were performed for all words presented in the four parallel sets of the EMOBACK task.

4.3.7 Statistical analysis

Results were analyzed using PASW (Predictive Analysis Soft Ware, Version 18.0, Chicago: SPSS Inc., Illinois, USA). Accuracy was defined as the ratio of correct responses (hits and correct rejections) to total number of stimuli. Mean reaction times of correct responses were additionally analyzed. In order to investigate the impact of emotional content on task performance independent of stimulation, one-way analyses of variance (ANOVAs) for the factor Emotion (fear, anger, neutral) were applied for accuracy and reaction times at baseline. To analyze stimulation effects,

repeated measures ANOVAs were applied for accuracy and reaction times with the factors tDCS priming (anodal, cathodal), rTMS (active, sham), Emotion (fear, anger, neutral) and Time (pre, post). To evaluate changes in subjects' current emotional state, repeated measures ANOVAs were applied for all MDBF subscales with the factors tDCS priming (anodal, cathodal), rTMS (active, sham) and Time ($T_{pre,}$ T_{post}). Furthermore, individual valence and arousal ratings of the stimulus material were analyzed separately in ANOVAs with the factors tDCS priming (anodal, cathodal), rTMS (active, sham), Emotion (fear, anger, neutral). For all analyses, the two-tailed threshold of significance was set at $p < 0.05$. If ANOVAs revealed significant main or interaction effects, further statistical analyses were conducted using contrasts or simple effects.

4.4 Results

4.4.1 Task performance

Baseline measurement:

A significant main effect of Emotion was found at baseline [$F(2,28) = 3.61$, $p < 0.05$, $\eta^2 = 0.21$] indicating impaired task accuracy for stimuli with negative valence. In comparison to neutral words, participants performed significantly less accurate for fear-related [$F(1,14) = 5.43$, $p < 0.05$, $\eta^2 = 0.28$] and anger-related words [$F(1,14) = 8.67$, $p < 0.05$, $\eta^2 = 0.38$]. With regard to reaction times, no significant effect of emotional content was found.

Stimulation effects:

The ANOVA on accuracy revealed a significant Emotion by Time interaction [$F(2,28) = 10.21$, $p < 0.001$, $\eta^2 = 0.42$]. Task accuracy increased significantly for fear-related words [$F(1,14) = 14.24$, $p < 0.05$, $\eta^2 = 0.50$] and decreased for neutral words [$F(1,14) = 5.34$, $p < 0.05$, $\eta^2 = 0.28$] across stimulation conditions (Fig. 14).

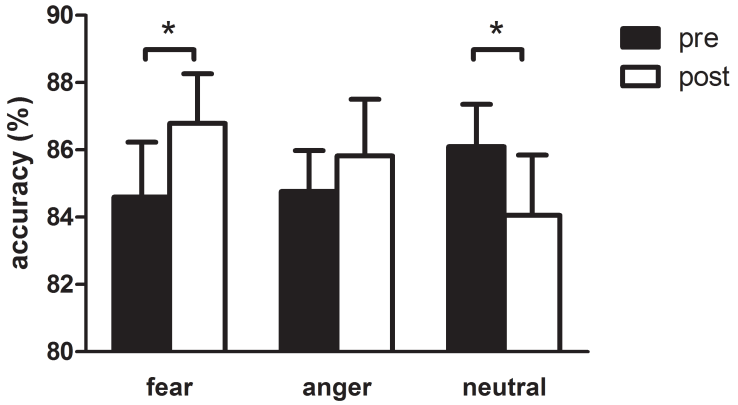

Fig. 14. Emotion-dependent task accuracy at baseline (pre) and after stimulation across conditions (post).

With regard to specific stimulation effects, there was a trendwise tDCS priming by Emotion interaction [$F(2,28) = 2.70$, $p = 0.085$, $\eta^2 = 0.16$]. To further explore this interaction we conducted ANOVAs for each emotion condition separately. For anger-related words, the threefold interaction tDCS priming by rTMS by Time almost reached significance [$F(1,14) = 4.51$, $p = 0.052$, $\eta^2 = 0.24$]. Further analyses of changes in task performance from baseline revealed converse rTMS effects dependent on the polarity of preceding tDCS (Fig. 15). Contrasts showed that this anger-specific effect was driven by a trend towards higher task accuracy for subsequent sham rTMS as compared to active rTMS in the cathodal priming condition [$F(1,14) = 4.24$, $p = 0.059$, $\eta^2 = 0.23$].

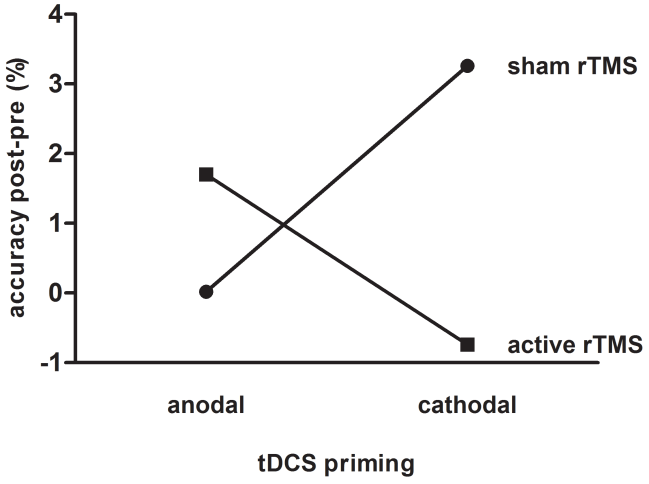

Fig. 15. Accuracy differences for anger-related words for the four stimulation conditions in the 2 (anodal/cathodal tDCS priming) x 2 (active/sham rTMS) design.

The ANOVA on reaction times revealed a significant main effect of Emotion [$F(2,28) = 31.85$, $p < 0.001$, $\eta^2 = 0.70$] and a significant Emotion by Time interaction [$F(2,28) = 11.6$, $p < 0.001$, $\eta^2 = 0.45$], indicating differences between emotion conditions across stimulation conditions. Contrasts showed that participants responded generally slower to fear-related words than to anger-related [$F(2,13) = 64.83$, $p < 0.001$, $\eta^2 = 0.91$] and neutral words [$F(2,13) = 64.83$, $p < 0.001$, $\eta^2 = 0.91$]. Over time, reaction times decreased for neutral words [$F(1,14) = 5.12$, $p < 0.05$, $\eta^2 = 0.27$] and trendwise for anger-related words [$F(1,14) = 4.08$, $p = 0.063$, $\eta^2 = 0.23$] across stimulation conditions. No effects of specific stimulation conditions were found for reaction times. Accuracy and reaction times at baseline (pre) and after stimulation (post) are reported in Table 7, separated for emotion conditions.

Tab. 7. EMOBACK task performance separated for emotion conditions (fear, anger, neutral) at baseline (pre) and after stimulation (post).

				Fear	Anger	Neutral
		tDCS	rTMS	M (SE)	M (SE)	M (SE)
Accuracy (%)	Pre	Anodal	Active	82.3 (1.9)	83.3 (1.4)	85.9 (1.7)
			Sham	85.9 (1.9)	86.1 (1.5)	87.8 (1.2)
		Cathodal	Active	85.3 (1.8)	85.7 (1.5)	85.4 (1.6)
			Sham	85.0 (2.1)	83.9 (1.8)	85.3 (1.4)
	Post	Anodal	Active	85.6 (1.6)	85.0 (1.7)	83.9 (2.0)
			Sham	86.6 (2.0)	86.2 (2.3)	85.4 (2.0)
		Cathodal	Active	87.0 (1.8)	85.0 (1.7)	82.7 (2.2)
			Sham	87.9 (1.6)	87.1 (2.1)	84.1 (2.0)
Reaction times (ms)	Pre	Anodal	Active	527.3 (40.3)	524.1 (38.4)	523.4 (41.3)
			Sham	535.1 (45.3)	535.3 (48.0)	538.8 (47.3)
		Cathodal	Active	535.9 (41.5)	515.2 (39.3)	521.3 (41.8)
			Sham	533.8 (46.7)	536.4 (46.3)	530.6 (46.1)
	Post	Anodal	Active	530.7 (35.4)	506.8 (37.2)	505.4 (40.6)
			Sham	549.1 (41.8)	524.1 (41.2)	523.1 (43.8)
		Cathodal	Active	531.4 (37.9)	503.4 (38.3)	509.2 (37.0)
			Sham	551.0 (41.5)	524.5 (40.9)	515.2 (38.8)

4.4.2 Control variables

No correlations were found between individual task performance (at baseline and after stimulation) and all assessed personality traits (Table 8).

Tab. 8. Sample characteristics.

		M (SD)
MWT-B	IQ	100.9 (6.2)
NEO-FFI	Neuroticism	16.4 (6.2)
	Extraversion	28.7 (4.8)
	Openness	32.7 (5.7)
	Agreeableness	33.0 (5.6)
	Conscientiousness	32.2 (7.1)
STAI-T		34.6 (5.4)
STAXI-T		7.9 (2.9)
BIS	Anxiety	2.2 (0.5)
	Frustration	2.2 (0.6)
BAS	Drive	3.3 (0.4)
	Gratification	3.5 (0.3)

M Mean, SD standard deviation, IQ Intelligence Quotient, MWT-B Mehrfachwahl Wortschatz Intelligenztest (verbal intelligence test), NEO-FFI NEO Five-Factor Inventory, STAI State-Trait Anxiety Inventory, STAXI State-Trait Anger Expression Inventory, BIS Behavioral Inhibition System, BAS Behavioral Approach System.

With regard to potential stimulation effects on participants' emotional state, ANOVAs on the MDBF scores revealed a main effect of Time on the wakefulness-sleepiness subscale [$F(1,14) = 10.55$, $p < 0.05$, $\eta^2 = 0.43$]. Participants felt in general more tired at the end of an experimental session. Furthermore, a main effect of tDCS priming was found on the calmness-restlessness subscale [$F(1,14) = 6.28$, $p < 0.05$, $\eta^2 =$

0.31], indicating stronger feelings of restlessness after anodal tDCS followed by active rTMS. Importantly, there were no mood changes caused by any of the four stimulation conditions. Means and standard deviations of the MDBF scores are shown in Table 9.

Tab. 9. Mood assessment before and after stimulation.

		Elevated – depressed mood		Wakefulness - sleepiness		Calmness - restlessness	
		Pre	Post	Pre	Post	Pre	Post
tDCS	rTMS	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Anodal	Active	16.5 (2.5)	15.1 (4.3)	14.1 (3.1)	11.9 (4.1)	16.0 (3.1)	15.1 (3.2)
	Sham	16.7 (2.1)	15.7 (3.8)	14.6 (3.0)	12.0 (3.4)	16.2 (2.9)	16.3 (2.7)
Cathodal	Active	16.8 (2.1)	16.7 (2.0)	13.8 (2.7)	13.1 (2.2)	17.1 (2.0)	16.9 (2.4)
	Sham	17.2 (2.0)	16.6 (2.6)	14.8 (2.9)	13.0 (3.0)	16.3 (2.8)	16.9 (2.5)

M Mean, SD standard deviation.

4.4.3 Word ratings

ANOVAs on individual word ratings revealed a main effect of Emotion on both valence [fear: -0.7 ± 0.4, anger: -0.9 ± 0.1, neutral: 0.2 ± 0.3; $F(2,28) = 61.78$, $p < 0.001$, $\eta^2 = 0.82$] and arousal [fear and anger: 2.6 ± 0.2; neutral: 1.9 ± 0.7; $F(2,28) = 25.81$, $p < 0.001$, $\eta^2 = 0.65$]. Contrasts showed that in comparison to neutral words, both fear- and anger-related words were rated more unpleasant [$F(1,14) = 42.90$, $p < 0.001$, $\eta^2 = 0.76$ and $F(1,14) = 112.96$, $p < 0.001$, $\eta^2 = 0.89$] and more arousing [$F(1,14) = 38.45$, $p < 0.001$, $\eta^2 = 0.73$ and $F(1,14) = 22.30$, $p < 0.001$, $\eta^2 = 0.61$]. Between fear- and anger-related words, a significant difference was found for valence [$F(1,14) = 10.00$, $p < 0.05$, $\eta^2 = 0.42$], indicating higher negative ratings for anger-related words. No stimulation effects on valence or arousal ratings were found.

4.5 Discussion

This study aimed to investigate state-dependent prefrontal rTMS effects on the performance in an emotional working memory task. By including fear- and anger-related words in a n-back paradigm we were additionally able to assess the interface between working memory and emotion as well as potential hemispheric lateralization of emotion processing. To our knowledge, this is the first study to explore the influence of tDCS priming followed by rTMS on cognitive-affective functions in healthy participants.

First of all, we found a detrimental effect of negative emotional content on working memory performance independent of stimulation. At baseline, participants responded less accurately to both fear- and anger-related words than to neutral words. This finding is in line with previous studies demonstrating that negative emotional content can impair task performance in n-back paradigms (Kensinger and Corkin 2003; Lindström and Bohlin 2012; Perlstein et al. 2002). It has been argued that emotionally salient stimuli capture and hold attention, resulting in increased task demands for higher executive functions such as working memory (Lindström and Bohlin 2012).

After tDCS priming and subsequent rTMS over the right DLPFC, task accuracy increased for fear-related words and decreased for neutral words across stimulation conditions. No changes in reaction times were found for fear-related words, whereas participants responded faster to neutral words. A potential mechanism underlying our results might be seen in an inhibition of the right DLPFC across stimulation conditions. According to the motivational direction model (Harmon-Jones 2004; Harmon-Jones et al. 2010) and in line with our previous study (Weigand et al. 2013), reduced activation of the right DLPFC might have influenced the processing of fear-related words exclusively. In line with this model, previous findings indicate that low-frequency rTMS over the right DLPFC reduces vigilant attention to fear-related stimuli (van Honk et al. 2002). Considering a detrimental effect of negative emotional content on working memory (Kensinger and Corkin 2003; Lindström and Bohlin 2012; Perlstein et al. 2002), which is supported by our baseline measurement, the inhibition of fear-related stimuli might have enhanced task performance in our study through a reduced attentional bias, and consequently a prioritized processing of task-relevant

information. With regard to the stimulation-induced decrease in task accuracy for neutral words, a potential explanation might be seen in the bilateral involvement of the DLPFC in the central executive of the working memory system (Smith and Jonides 1999). The n-back paradigm used in our study involves a number of key processes within working memory including monitoring, updating and manipulating the remembered information (Owen et al. 2005). Comparable to the neutral condition in our EMOBACK task, previous research demonstrated that inhibitory stimulation significantly impaired task performance in a non-emotional verbal n-back task when applied to the left or right DLPFC (Mottaghy et al. 2000). Importantly, our result of a speeding of response accompanying the decrease in accuracy for neutral words might appear to reflect a speed-accuracy tradeoff induced by the stimulation. However, a general speed-accuracy tradeoff is unlikely because trendwise speeding of response was also found for anger-related words, but without concomitant decrease in accuracy. In order to ensure that a speed-accuracy trade-off had not occurred in the neutral condition, we calculated the correlation between accuracy and RTs. We did not find a correlation, ruling out a speed–accuracy trade-off that might have accounted for the described rTMS effects. Alternatively, our results showing shorter reaction times despite decreased task accuracy for neutral words might be explained by previous findings suggesting that a diminution in cortical excitability impairs the ability to identify target stimuli, but, once identified, improves the perception due to a focusing effect (Antal et al. 2004; Nitsche et al. 2012).

With regard to task performance for anger-related words, our results showed more specific stimulation effects. Whereas active rTMS over the right DLPFC increased task accuracy when applied after anodal tDCS, it slightly decreased after cathodal tDCS. These converse stimulation effects in dependence on the polarity of preceding tDCS are in line with neurophysiological studies from the motor cortex indicating state-dependent effects of rTMS application (Cosentino et al. 2012; Iyer et al. 2003; Lang et al. 2004; Siebner et al. 2004). Further analyses of our data revealed, however, that the interaction between tDCS priming and rTMS was driven by enhanced task accuracy of subsequent sham rTMS as compared to active rTMS in the cathodal priming condition. Thus, participants responded to anger-related words more accurately after inhibitory cathodal tDCS applied over the right DLPFC. Based on the motivational direction model (Harmon-Jones 2004; Harmon-Jones et al. 2010), we would have expected the opposite effect for anger-related words, namely a

decrease in task accuracy after inhibiting the right DLPFC. Previous findings showed that low-frequency rTMS applied over the right DLPFC shifts the anterior asymmetry in brain activation to the left through a contralateral excitation (Nahas et al. 2001; Schutter et al. 2001) and increases selective attention to anger-related stimuli (d'Alfonso et al. 2000). However, in our previous study (Weigand et al. 2013), no anger-related effects were found in the EMOBACK task after both left- or right-sided low-frequency rTMS of the DLPFC.

Importantly, our stimulation effects were not accompanied by systematic mood changes across stimulation conditions. This finding supports previous research showing no influence on the emotional state in healthy volunteers after prefrontal stimulation using low-frequency rTMS (Grisaru et al. 2001; Jenkins et al. 2002) or tDCS (Nitsche et al. 2012; Koenigs et al. 2009; Plazier et al. 2012). Our participants, however, reported significant stronger feelings of restlessness after anodal tDCS followed by active rTMS. This stimulation condition consists of an active double and direct stimulation of the DLPFC, making the sensation accompanying the stimulation more discernible than the other stimulation conditions. It can be speculated that stronger feelings of restlessness may have influenced otherwise more specific stimulation effects by disturbing task performance.

Because emotional valence and arousal may be controlled by different neural systems (Garavan et al. 2001; Gerber et al. 2008), an advantage of this study is the carefully matched selection of words with equal valence and arousal levels for fear- and anger-related words according to the BAWL norms. We additionally controlled our stimuli sets with regard to lexical and sublexical dimensions whose relevance has been shown in tasks relying on word material (Graf et al. 2005). To further control our stimulus material, we asked participants to rate valence and arousal of all presented words individually. As expected, the results of the word ratings of our sample revealed that participants perceived anger- and fear-related words as more unpleasant and arousing relative to neutral words. Fear-and anger-related words did not differ in arousal ratings; however, anger-related words were rated more negatively than fear-related words. To further explore this finding, it would be reasonable to include individual word ratings to assess the distinct emotions fear and anger in future studies. In the present study, distinct emotion ratings could have clarified whether the selected anger-related words from the DENN-BAWL were

possibly not correctly perceived and therefore, not associated with the left DLPFC as suggested by previous findings (d'Alfonso et al. 2000; Schutter et al. 2001). Importantly, our participants rated the stimulus material equally across stimulation conditions indicating that the reported stimulation effects cannot be explained by differences in perceived valence or arousal levels of our stimuli. Moreover, we controlled for personality traits that are associated with a potential influence on emotion processing (Balconi and Mazza 2010; Bishop 2009; Harmon-Jones et al. 2010; Shackman et al. 2006; van Honk et al. 2001) and might influence stimulation effects (Balconi and Ferrari 2012; Wassermann et al. 2001). However, a number of additional factors are likely to influence individual responses to brain stimulation (for a review, see Ridding and Ziemann 2010) and need to be further explored in future research.

4.6 Conclusion

In summary, we demonstrated that the withdrawal-related emotion fear is associated with the right DLPFC and seems to be differentially processed as compared to the approach-related emotion anger. This finding is in line with our previous study (Weigand et al. 2013) and further supports a frontal asymmetry of emotion processing as proposed by the motivational direction model (Harmon-Jones 2004; Harmon-Jones et al. 2010). No general state-dependent effects of prefrontal rTMS on working memory were found. Furthermore, our data contribute to clarifying the interaction between working memory and emotion by supporting previous findings of a detrimental effect of negative emotional content (Kensinger and Corkin 2003; Lindström and Bohlin 2012; Perlstein et al. 2002). Future interleaved TMS/tDCS-fMRI studies are needed in order to causally investigate neural mechanisms underlying lateralized emotion processing and state-dependent prefrontal stimulation effects on higher cognitive functions.

5 Effects of Intranasal Oxytocin prior to Encoding and Retrieval on Recognition Memory

Weigand A, Feeser M, Gärtner M, Brandt E, Fan Y, Fuge P, Böker H, Bajbouj M * & Grimm S * (2013). Psychopharmacology 227(2):321-9

http://dx.doi.org/10.1007/s00213-012-2962-z

5.1 Abstract

The neuropeptide oxytocin (OXT) has been shown to modulate a variety of human social behaviors. However, little is known about its impact on emotional memory processing. Previous research demonstrated both memory-enhancing and memory-impairing oxytocinergic effects. We investigated the influence of a single (prior to encoding) and a repeated (prior to encoding and retrieval) intranasal administration of OXT on recognition memory for stimuli taken from the International Affective Picture System. In addition, we assessed the interaction of emotion regulation during encoding and OXT-induced memory effects. In a double-blind, placebo-controlled design, 80 healthy young males performed an emotion regulation task followed by a surprising recognition memory task after 60 min. Results show that repeated OXT administration significantly improved memory certainty for negative social stimuli. Regarding the influence of emotion regulation, the promnestic effect of OXT was more pronounced when participants had been instructed to increase their negative emotions during encoding. Our findings indicate that OXT facilitates the processing of negative social stimuli during memory encoding and retrieval, possibly by enhancing the perception of aversive aspects in social situations.

5.2 Introduction

Oxytocin (OXT), a neuropeptide originally known for its role in labor and maternal nurturing, has been shown to affect a variety of human social behavior (Campbell

2010; Heinrichs et al. 2009). Intranasal OXT application improves emotion recognition for facial expressions (e.g. Averbeck et al. 2011; Di Simplicio et al. 2009; Fischer-Shofty et al. 2010; Guastella et al. 2010; Lischke et al. 2012; Marsh et al. 2010; Schulze et al. 2011), increases emotional empathy (Hurlemann et al. 2010) and facilitates trust in social interactions (Baumgartner et al. 2008; Kosfeld et al. 2005). Moreover, OXT can induce anxiolytic effects by diminishing both cortisol and behavioral responses to social stress (Heinrichs et al. 2003). Regarding the underlying neurobiological mechanisms, the amygdala might be a key structure for the mediation of the prosocial effects of OXT (Domes et al. 2007; Kirsch et al. 2005; Riem et al. 2011). However, recent findings point to rather antisocial effects of OXT (Yamasue et al. 2012), such as increased envy and gloating (Shamay-Tsoory et al. 2009) as well as in-group favoritism and noncooperation towards potentially threatening out-groups (De Dreu et al. 2012a).

The potential of OXT as an enhancer for specific processes involved in memory has also been controversially discussed. Studies using facial stimuli found both a memory-enhancing (Guastella et al. 2008; Rimmele et al. 2009; Savaskan et al. 2008) and a memory-impairing effect (Herzmann et al. 2012). It has been suggested that the inconsistent OXT-induced effects on memory might be explained due to differences in the emotional expression of the faces (Herzmann et al. 2012). Most of the studies found that OXT particularly enhances the processing of positive facial expressions (Di Simplicio et al. 2009; Marsh et al. 2010; Schulze et al. 2011), resulting in higher memory performance for happy faces (Guastella et al. 2008). Findings are more inconsistent, however, with regard to the processing of negative emotions. For example, the recognition of angry and fearful expressions was found to be either facilitated (Fischer-Shofty et al. 2010; Savaskan et al. 2008) or impaired (Di Simplicio et al. 2009; Evans et al. 2010) by OXT administration. Conflicting results were also shown for neutral facial expressions, which were found to be associated with either no effect of OXT (Guastella et al. 2008; Savaskan et al. 2008) or a memory-impairing effect (Herzmann et al. 2012). Nevertheless, other studies found no influence of facial expression on oxytocinergic effects (Lischke et al. 2012; Rimmele et al. 2009). Interestingly, a recent study implemented social scenes in a surprising recall test and observed an OXT-induced bias towards remembering aversive social information by facilitating anterior insular responses despite reduced amygdala activity (Striepens et al. 2012). Regarding non-social stimuli, previous

studies described an amnestic (Herzmann et al. 2012) as well as no effect (Rimmele et al. 2009) of OXT on memory.

In view of these controversial effects of OXT, it has been proposed that OXT increases the salience of social cues (Averbeck 2010; Bartz et al. 2011) and enhances defensive responses in uncertain social contexts, suggesting that OXT can also be anxiogenic (Grillon et al. 2012). Growing evidence also indicates differential effects of OXT as a function of situational or personal characteristics (Bartz et al. 2011). For example, studies have found effects of OXT to be more pronounced in individuals with impaired emotion regulation abilities (Quirin et al. 2011) and in participants with high scores in alexithymia (Luminet et al. 2011), a multifaceted personality construct characterized by difficulties in identifying, decoding and communicating one's own emotional state and emotional aspects of social interaction processes (Franz et al. 2008).

In animal studies, OXT has been shown to improve only social but not non-social memory. Social memory in rodents is examined through the ability to recognize a conspecific during the second encounter as compared to the first (Bielsky and Young 2004; Ferguson et al. 2002). Interestingly, in an OXT receptor knock-out mouse model, the resulting deficit in social recognition was restorable with the injection of OXT only before and not after encoding (Ferguson et al. 2000).

Most of the human studies investigating OXT-induced effects on memory administered the drug prior to the acquisition phase of the experiment (Di Simplicio et al. 2009; Guastella et al. 2008; Herzmann et al. 2012; Rimmele et al. 2009; Striepens et al. 2012). Therefore, OXT affects encoding and may additionally influence memory consolidation. Savaskan et al. (2008) used post-acquisition OXT to exclusively investigate consolidation effects. They administered OXT immediately after the acquisition phase and tested the memory performance after 30 min and 24 h. Promnestic effects of OXT were found in both retention intervals. To our knowledge, no studies have investigated memory effects of a repeated OXT application, administered prior to both encoding and retrieval.

Brain imaging studies have shown that the amygdala plays a critical role for the encoding (Adolphs et al. 2005; Kensinger and Schacter 2005) as well as for the retrieval of emotional memories (Sharot et al. 2004). In addition, Erk et al. (2010)

investigated the effects of emotion regulation on recognition memory and found that the amygdala activation during retrieval depends on the emotional engagement during encoding. Their findings revealed stronger amygdala involvement during recognition memory of negative stimuli when emotions had not been downregulated during encoding. Thus, given the evidence that OXT has been found to reduce amygdala activation (Domes et al. 2007; Kirsch et al. 2005; Riem et al. 2011), OXT may influence recognition memory through its influence on emotion regulation processes during the acquisition of emotional stimuli.

Based on these considerations, the primary aim of this study was to assess the effects of a single (prior to encoding) and a repeated (prior to encoding and retrieval) OXT application on memory performance for stimuli with different emotional valence. We hypothesized that especially the repeated OXT administration may enhance oxytocinergic effects on recognition memory. Additionally, we were interested in a possible interaction of OXT-induced effects and emotion regulation on memory performance.

5.3 Methods

5.3.1 Subjects

A total of 80 healthy male volunteers, aged between 18 and 42 years (mean age 27.9 ± 4.7), participated in the study. All subjects were without any neurological or psychiatric condition, as determined by the short version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (SCID, Wittchen et al. 1997). A verbal intelligence test (Mehrfachwahl Wortschatz Intelligenztest, MWT; Lehrl et al. 1995) showed that IQ levels of all subjects were in or above the range of the norm (mean IQ score 108.8 ± 12.0). Written informed consent was obtained and subjects were paid for participation. The study was approved by the Institutional Review Board of the German Psychological Society and conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

5.3.2 Study Design

In a double-blind, placebo-controlled, between-subjects design, participants were randomly assigned to groups that received either OXT (Syntocinon Spray, Novartis, Basel, Switzerland) or a placebo intranasally. Consistent with previous studies (e.g. Gamer and Büchel 2012; Hurlemann et al. 2010; Labuschagne et al. 2010; Marsh et al. 2010), participants self-administered 3 puffs per nostril with a dose of 24 international units (IU).

Two tasks were used in this study (adapted from Erk et al. 2010): first, an emotion regulation task and second, a recognition memory task, which had not been announced previously and therefore, came as a surprise to the subjects. For stimulus presentation we used Presentation® (Version 14.5., Neurobehavioral Systems Inc., San Francisco, CA, USA). All participants received either OXT (N=40) or a placebo (N=40) 45 min before the emotion regulation task (Born et al. 2002). Additionally, half of the participants received a second administration of the same substance (OXT: N=20, placebo: N=20) 45 min before the recognition memory task. In this way, four different conditions with 20 subjects in each experimental group were realized in this study. The experimental procedure is illustrated in Figure 16.

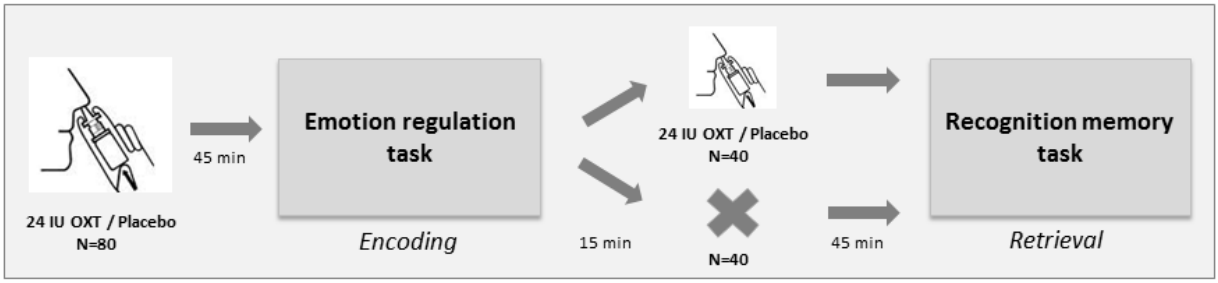

Fig. 16. Experimental procedure with the emotion regulation task followed by the surprising recognition memory task after 60 min.

5.3.3 Emotion regulation task

In the emotion regulation task, participants were presented with 60 negative, 20 positive and 20 neutral pictures taken from the International Affective Picture System (IAPS; Lang et al. 2008). Sets of 20 negative pictures each were assigned to the three regulation conditions, which were announced by the instruction word “upregulate”, “downregulate” or “maintain”, respectively (adapted from Ochsner et al. 2004). Negative stimuli were matched between regulation conditions for mean valence (V) and arousal (A) values according to the IAPS norms (upregulate: V=2.6 ± 0.7, A=5.6 ± 0.9; downregulate: V=2.7 ± 0.9, A=5.6 ± 1.0, maintain: V=2.9 ± 0.7, A=5.5 ± 0.8). Positive and neutral pictures were only presented in the maintain condition (positive: V=7.1 ± 0.4, A=5.3 ± 0.6, neutral: V=5.2 ± 0.3, A=3.0 ± 0.7).

Subjects were intensively trained to upregulate their emotions by imagining a worse outcome than suggested by the picture, to downregulate their emotions by imagining a better outcome than suggested by the picture, and to maintain their emotions by permitting spontaneous feelings, without regulating their emotions. The instruction words were shown in the middle of the screen for 1 sec followed by the picture which was presented for 8 sec. After each picture presentation, subjects were prompted to rate the valence of the picture on a 9-point scale (0=very unpleasant, 8=very pleasant). During the interstimulus interval (ISI), a fixation cross appeared for 2 sec. A total of 100 pictures were presented in a randomized order. The duration of the emotion regulation task was approximately 30 min. Participants were unaware of a subsequent recognition memory test 60 min later (Sharot et al. 2004).

5.3.4 Recognition memory task

In the recognition memory task (adapted from Sharot et al. 2004), the 100 pictures from the emotion regulation task and 50 new pictures were presented randomly. The new pictures contained 30 negative, 10 positive and 10 neutral pictures and were matched with the previously seen pictures with respect to mean valence (V) and arousal (A) values for the three valence conditions (new negative: V=2.8 ± 0.7, A=5.6 ± 0.7, new positive: V=7.0 ± 0.6, A=5.1 ± 0.8, new neutral: V=5.2 ± 0.3, A=3.0 ± 0.5).

Participants were asked to make remember/know/new judgments (Tulving 1985). They were instructed to respond “remember” when they could recall details about the picture or contextual information and respond “know” when they were convinced that the picture was presented in the emotion regulation task without recalling any details. Subjects had to respond “new” when they were convinced that the picture had not been shown before. This recognition memory task allows to distinguish between two distinct memory processes, often referred to as recollection (remember responses) and familiarity (know responses) (Yonelinas 2002). The pictures were presented for 8 sec followed by the judgment task. During the interstimulus interval (ISI), a fixation cross appeared for 2 sec. In total, the duration of the recognition memory task was 20 min.

5.3.5 Control variables

To ensure group matching with regard to interindividual differences in characteristics that might influence oxytocinergic effects, the following questionnaires were completed by all participants before testing: The Emotion Regulation Questionnaire (ERQ; Gross and John 2003) and the Bermond-Vorst Alexithymia Questionnaire (BVAQ; Vorst and Bermond 2001). The ERQ investigates two common emotion regulation strategies with a 10 item self-report instrument: Expressive suppression (four items) and Reappraisal (six items). Each item consists of a 7-point Likert scale (1=strongly disagree; 7=strongly agree) and higher scores reflect a stronger habitual use of the particular strategy. The BVAQ assesses alexithymia as a multifaceted personality construct and consists of five dimensions targeting basic social-emotional competencies: Verbalizing, fantasizing, identifying, emotionalizing, and analyzing. Each dimension is measured by eight items on a 5-point Likert scale (1=strongly disagree; 5=strongly agree) with high scores indicating high proneness to alexithymia.

5.3.6 Statistical Analysis

Memory task performance (hit and miss rates, according to Erk et al. 2010) was analyzed using repeated measures analyses of variance (ANOVAs) with the within-

subjects factors Valence (positive, negative, neutral) and Memory certainty (remember, know) as well as Regulation (up, down). Between-subjects factors were Treatment (OXT, Placebo) and Application (single, repeated). Reaction times for correctly recognized pictures were additionally analyzed by averaging remember and know responses. For the individual emotional ratings, one-way ANOVAs with the within-subjects factor Valence (positive, negative, neutral) and Regulation (up, down) and the between-subjects factor Treatment (OXT, Placebo) were applied. Greenhouse-Geisser corrections were applied where appropriate. Further statistical analysis was conducted using t-test comparisons. All tests were two-tailed and the significant threshold was set at a probability of $p < .05$. Statistical analyses were carried out using PASW (Predicitive Analysis SoftWare, Version 18.0, Chicago: SPSS Inc., Illinois, USA).

5.4 Results

5.4.1 Demographics and individual characteristics

Data from three subjects were classified as outliers due to poor task performance (hits < 70%) and therefore excluded from analyses. There were no significant differences between subjects who received a single application and those who received a repeated application (OXT vs. placebo) with respect to age, years of education, verbal intelligence (MWT) and alexithymia scores (BVAQ). Regarding the emotion regulation abilities (ERQ), participants in the group with a single OXT application scored significantly higher on the subscale Reappraisal in comparison to the single Placebo application. No ERQ differences were found between the groups of repeated substance application. The characteristics of the four experimental groups are reported in Table 10.

Tab. 10. Demographics and individual characteristics.

		Single application				t [a]	p
		Oxytocin N=20		Placebo N=19			
		M	SD	M	SD		
Age		30.0	4.8	29.3	4.4	-0.466	0.644
Years of education [b]		13.5	2.3	12.8	0.6	-1.325	0.194
MWT - IQ scores		110.4	15.6	104.8	10.9	-1.270	0.212
ERQ	Reappraisal	4.9	1.1	4.2	1.0	-2.044	0.048
	Suppression	3.8	1.1	3.7	1.0	-0.301	0.765
BVAQ	Verbalizing	21.9	7.2	23.4	6.6	0.683	0.499
	Fantasizing	19.2	5.5	20.8	6.7	0.863	0.394
	Identifying	17.0	5.2	19.5	4.9	1.562	0.127
	Emotionalizing	22.8	4.4	23.1	3.9	0.190	0.850
	Analyzing	17.1	4.0	19.5	7.0	1.305	0.200
	total score	98.0	16.4	106.3	19.0	1.472	0.150
		Repeated application				t [a]	p
		Oxytocin N=18		Placebo N=20			
		M	SD	M	SD		
Age		25.2	3.1	27.8	5.0	1.950	0.059
Years of education [b]		12.7	1.0	13.2	0.8	1.477	0.149
MWT - IQ scores		107.4	11.3	110.9	12.2	0.890	0.379
ERQ	Reappraisal	4.5	1.0	4.3	1.1	-0.539	0.594
	Suppression	3.5	0.9	3.7	1.1	0.632	0.531
BVAQ	Verbalizing	21.9	5.6	23.6	8.2	0.741	0.463
	Fantasizing	16.9	5.0	20.1	7.6	1.470	0.150
	Identifying	18.6	6.1	20.4	3.9	1.116	0.272
	Emotionalizing	21.8	3.6	23.9	3.2	1.880	0.068
	Analyzing	18.5	4.6	20.5	6.9	1.033	0.308
	total score	97.7	16.0	108.5	6.9	1.772	0.085

M Mean, SD standard deviation, IQ Intelligence Quotient, MWT Mehrfachwahl Wortschatz Intelligenztest (verbal intelligence test), ERQ Emotion Regulation Questionnaire, BVAQ Bermond–Vorst Alexithymia Questionnaire.

[a] Independent samples t-tests, two-tailed.

[b] Data missing from three subjects (N=2 single OXT application, N=1 repeated placebo application).

5.4.2 Influence of OXT on memory performance

The ANOVA for the hit rates revealed a significant interaction for the factors Memory certainty, Valence, Treatment and Application [$F(2,146) = 3.50$, $p < .05$, $\eta^2 = .05$]. To further clarify this interaction and in order to explore dose- and time- related effects of OXT on memory performance, ANOVAs were performed separately for single and repeated application. The ANOVA for the repeated substance application revealed a significant Valence by Memory certainty by Treatment interaction [$F(2,72) = 3.61$, $p < .05$, $\eta^2 = .09$]. Further post hoc comparisons revealed that this effect was driven by a significantly improved memory certainty (more remember and less know responses) for negative pictures in those participants who had been administered OXT [remember negative: $t(36) = -2.42$, $p < .05$, know negative: $t(36) = 2.17$, $p < .05$]. The results of the valence comparisons between the repeated application of OXT and placebo are presented in Figure 17a (remember responses) and 17b (know responses).

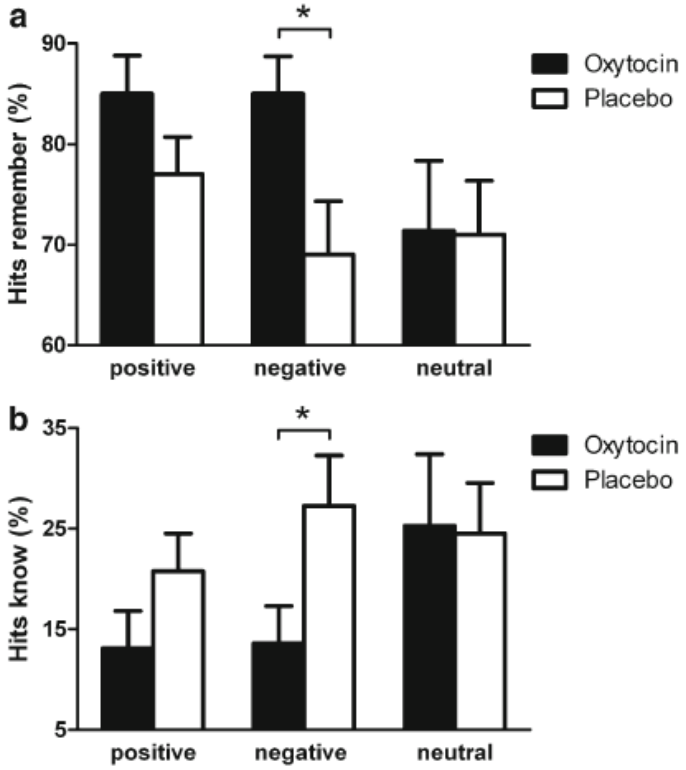

Fig. 17. a and b. Hit rates for (a) remember and (b) know responses in the three valence conditions after repeated application of oxytocin compared to placebo. Asterisks indicate significant post hoc comparisons ($p < .05$, two-tailed). Bars represent mean percent ± standard error of mean.

With regard to reaction times for correctly recognized pictures, the ANOVA for repeated substance application revealed a significant Valence by Treatment interaction [$F(2,72) = 3.37$, $p < .05$, $\eta^2 = .09$]. In line with the accuracy data, further t-test comparisons demonstrated significantly shorter reaction times only for negative pictures after the application of OXT in comparison to the control condition [OXT: 2876.2 ms ± 220.5 ms; placebo: 3106.8 ms ± 314.1 ms; $t(36) = 2.59$, $p < .05$]. No significant influence on memory performance could be found between the groups after single application of OXT and placebo.

With regard to the influence of emotion regulation on memory performance, the ANOVA performed for the hit rates after repeated substance application revealed a trend for a main effect of Regulation [$F(1,36) = 3.68$, $p = .06$, $\eta^2 = .09$] and a trend for the Memory certainty by Treatment interaction [$F(2,36) = 3.00$, $p = .09$, $\eta^2 = .08$]. Further t-test comparisons demonstrated a significant improvement in memory performance after OXT application compared to the control condition only in the upregulated condition for remember responses [$t(36) = 2.15$, $p < .05$]. In the upregulated condition for know responses, a trend for less know responses was found after OXT application [$t(36) = 1.95$, $p = .06$]. No significant differences in reaction times for correctly recognized pictures were observed in the respective comparisons after the repeated application of OXT. After single OXT or placebo administration, memory performance was not influenced by emotion regulation. Table 11 shows the hit and miss rates for all conditions.

Tab. 11. Results of the recognition memory task for all experimental conditions. Hit and miss rates are subdivided into remember and know responses.

Performance (%)			Single application			
			Oxytocin		Placebo	
			M	SE	M	SE
Hits Remember	Valence	pos	79.5	4.6	80.8	4.7
		neg	75.3	5.0	71.3	5.5
		neu	71.0	6.6	62.4	7.9
Hits Know		pos	18.3	4.1	17.1	4.6
		neg	20.8	4.3	24.5	5.6
		neu	24.0	5.7	31.8	7.3
Misses		pos	2.3	0.8	2.1	0.6
		neg	4.0	1.4	4.2	1.3
		neu	5.0	2.1	5.8	2.2
Hits Remember	Regulation	up	73.8	5.2	70.8	5.9
		down	73.0	5.0	71.6	5.1
Hits Know		up	22.8	4.9	25.0	5.1
		down	24.0	4.8	23.4	5.8
Misses		up	3.5	1.1	4.2	1.8
		down	3.0	0.9	5.0	2.4
Performance (%)			Repeated application			
			Oxytocin		Placebo	
			M	SE	M	SE
Hits Remember	Valence	pos	85.0	3.8	77.0	3.7
		neg	85.0	3.7 *	69.0	5.3
		neu	71.4	7.0	71.0	5.4
Hits Know		pos	13.1	3.7	20.8	3.7
		neg	13.6	3.7*	27.3	5.0
		neu	25.3	7.1	24.5	5.0
Misses		pos	1.9	0.8	2.3	0.7
		neg	1.4	0.5	3.8	1.0
		neu	3.3	1.1	4.5	1.8
Hits Remember	Regulation	up	83.6	3.5 *	70.8	4.7
		down	82.5	4.3	73.5	5.1
Hits Know		up	15.3	3.5	27.0	4.8
		down	15.3	4.1	22.8	4.6
Misses		up	1.1	0.6	2.3	0.8
		down	2.2	0.8	3.8	1.1

* indicates significant ($p<.05$) higher memory certainty (more remember and less know responses) in the oxytocin compared to the placebo group.

5.4.3 Influence of valence on memory performance

Regarding valence effects on memory performance independently of OXT administration, the ANOVA for the hit rates revealed a significant main effect of Valence [$F(2,146) = 4.20$, $p < .05$, $\eta^2 = .05$] and a significant Valence by Memory certainty interaction [$F(2,146) = 13.18$, $p < .001$, $\eta^2 = .15$] indicating that memory performance was significantly influenced by picture valence. Positive and negative stimuli were better recognized (more remember and less know responses) in comparison to neutral pictures [remember positive: $t(76) = 4.83$, $p < .001$; remember negative: $t(76) = 2.60$, $p < .05$; know positive: $t(76) = 4.15$, $p < .001$; know negative: $t(76) = 2.27$, $p < .05$]. Positive stimuli showed a higher memory certainty than negative pictures [remember: $t(76) = 3.14$, $p < .05$; know: $t(76) = 2.43$, $p < .05$].

5.4.4 Emotional ratings

The ANOVAs applied for the individual valence ratings of the pictures revealed main effects for Valence [$F(2,152) = 553.37$, $p < .001$, $\eta^2 = .88$] and Regulation [$F(1,76) = 94.21$, $p < .001$, $\eta^2 = .55$]. Post-hoc comparisons demonstrated that valence ratings systematically varied with emotion condition: positive pictures were rated significantly more pleasant than negative [positive: 5.9 ± 0.7, negative: 2.7 ± 0.5, $t(76) = 27.07$, $p < .001$] and neutral pictures [neutral: 4.5 ± 0.5, $t(76) = 17.56$, $p < .001$]. Neutral pictures were rated significantly more pleasant than negative pictures [$t(76) = 20.58$, $p < .001$]. Furthermore, downregulated pictures were rated significant more pleasant than upregulated pictures [downregulate: 3.2 ± 0.6, upregulate: 2.4 ± 0.6, $t(76) = 9.71$, $p < .001$]. These results indicate that the stimuli sets were successfully matched according to the IAPS norms and that the participants had thoroughly understood the instruction of the emotion regulation task. There was no significant effect of OXT administration on the emotional ratings.

5.5 Discussion

The present study aimed at investigating the effects of a single (prior to encoding) and a repeated (prior to encoding and retrieval) OXT administration on recognition memory of social stimuli. In addition, the study assessed the potential interaction of emotion regulation processes and OXT-induced memory effects. Participants performed an emotion regulation task followed by a surprising recognition memory task after 60 min.

As hypothesized, we found that OXT administered prior to both acquisition and retrieval significantly improved recognition memory. Importantly, this effect was driven by enhanced memory certainty (more remember and less know responses) for pictures with a negative emotional valence. Regarding the influence of emotion regulation on recognition memory, our results revealed a significant improvement in memory certainty (more remember responses) when participants had been instructed to increase their negative emotions during encoding.

Our results are in line with previous studies suggesting that OXT facilitates the processing of negative stimuli (Fischer-Shofty et al. 2010; Savaskan et al. 2008; Striepens et al. 2012). However, Fischer-Shofty et al. (2010) and Striepens et al. (2012) found a specific role for OXT after a single drug application prior to encoding, whereas Savaskan et al. (2008) administered OXT immediately after encoding. Other previous studies assessing oxytocinergic effects on emotion recognition also realized pre-encoding designs for OXT treatment (Di Simplicio et al. 2009; Guastella et al. 2008; Herzmann et al. 2012; Rimmele et al. 2009). To our knowledge, the present study provides the first experiment with repeated OXT application, administered prior to both encoding and retrieval.

Most previous studies which investigated emotional memory-effects of OXT used facial expressions as social stimuli. Human faces showed direct gaze and were presented in an elliptic mask (Herzmann et al. 2012; Rimmele et al. 2009), in a rectangular frame (Fischer-Shofty et al. 2010) or as a complete photograph (Guastella et al. 2008; Savaskan et al. 2008). Comparable to Striepens et al. (2012), we used emotional IAPS pictures showing social scenes, as we believed they would present more complex and realistic social situations. Neutral IAPS pictures served as

a control condition for the assessment of non-social recognition memory. In addition to the stimuli used in the free-recall experiment by Striepens et al. (2012), we also implemented positive social pictures in order to investigate valence-specific memory effects of OXT.

In contrast to previous research (Guastella et al. 2008), we did not find a promnestic effect of OXT for positive stimuli after repeated OXT application as compared to the placebo condition. This may be explained due to a potential ceiling effect in memory performance for positive stimuli in the placebo group. In fact, memory certainty for positive as compared to negative stimuli did not differ within the OXT group after repeated substance application, whereas positive stimuli showed a higher memory certainty as compared to negative stimuli within the placebo group.

A recent study investigated oxytocinergic effects on basic evaluative processes for IAPS pictures (Norman et al. 2011). The authors showed that OXT selectively decreased arousal ratings to human social threat, regardless of valence ratings. This is in line with our data of the subjective ratings of the participants that showed no influence of OXT on emotional valence during the emotion regulation task. Furthermore and also in line with our results, Norman et al. (2011) found no oxytocinergic effect on non-social IAPS pictures, demonstrating the selective influence of OXT to social stimuli.

Based on these considerations, a potential explanation for the present findings might be that OXT diminished emotional arousal for the negative IAPS pictures. Norman et al. (2011) suggested that reduced emotional arousal to social threat after OXT application may promote more elaborated processing of social interactions. However, Striepens et al. (2012) found no evidence for OXT affecting either arousal or valence ratings, challenging additionally the suggestion that OXT increases the salience of social cues (Averbeck 2010; Bartz et al. 2011). Interestingly, Striepens et al. (2012) demonstrated that OXT enhances the impact of aversive social stimuli by facilitating anterior insular responses and functional coupling between amygdala, anterior insula and inferior frontal gyrus.

Though rather speculative due to the lack of neuroimaging data, our finding of a promnestic effect of OXT for negative stimuli might be explained by reduced amygdala activation (Domes et al. 2007; Kirsch et al. 2005; Riem et al. 2011) and

increased insular responses (Striepens et al. 2012). Since the amygdala has been found to be crucially involved in encoding (Adolphs et al. 2005; Kensinger and Schacter 2005) as well as in retrieval of emotional memories (Sharot et al. 2004), the repeated OXT administration may influence amygdala activation during both processes. In line with Erk et al. (2010), emotion regulation during encoding may additionally modulate the amygdala activation during retrieval in our experiment. Since we found a memory-enhancing effect of OXT in the upregulated as compared to the downregulated condition, OXT may especially diminish the amygdala activation in the recognition memory task for negative stimuli when participants had been instructed to upregulate their emotions during encoding. Furthermore, potentially heightened insular activation after OXT application may increase feelings of uncertainty and risk arising from enhanced empathic responses, promoting approach and potentially protective behavior (Striepens et al. 2012).

Importantly, we found memory-enhancing effects of OXT only after repeated substance administration. In the present study, participants self-administered 24 IU OXT 45 min prior to both encoding and retrieval, separated by a time gap of 90 min. Recently, Huffmeijer et al. (2012) found that salivary concentrations of OXT remain elevated for more than two hours after intranasal administration of an even smaller dose of 16 IU OXT. Therefore, cumulative effects might be plausible in the present study and may explain our finding of enhanced memory certainty exclusively after repeated OXT application.

The memory-enhancing OXT effects in the present study occurred in the absence of significant differences in participant demographics and individual characteristics with regard to intelligence (MWT) or personality traits targeting basic social-emotional competencies (BVAQ). Regarding the emotion regulation abilities (ERQ), the only significant difference was found for the subscale Reappraisal between groups of single substance application, indicating that participants in the OXT condition showed a stronger habitual use of the respective emotion regulation strategy in comparison to the placebo condition. In our study, there was no significant enhancement in memory certainty after the single application of OXT. Thus, one might speculate that participants with impaired regulation abilities would have shown more pronounced effects of OXT, as suggested by Quirin et al. (2011).

There are a number of limitations to this study that are important to consider. First, we administered OXT either prior to encoding or prior to both encoding and retrieval, and we did not realize an experimental condition with the single application of OXT prior to retrieval. Therefore, we cannot discern whether the oxytocinergic effects shown in our study are due to the repeated application or whether these effects would also occur in the absence of OXT administration prior to encoding. Potential cumulative effects of OXT levels after repeated administration may be measured in salivary concentrations which have been recently suggested as a valuable biomarker for OXT (Huffmeijer et al. 2012; Weisman et al. 2012). Second, the emotional pictures in our study showed social sceneries, whereas the neutral stimuli were non-social. We did not include a neutral control condition with social sceneries, therefore it is not clear whether OXT would have improved social memory independently of its valence. Considering the norms of the IAPS pictures, however, only a few social scenes are perceived as completely neutral. Third, we implemented negatively valenced pictures in our experimental tasks without distinguishing discrete emotion categories. In future studies, it would be reasonable to additionally consider the picture content in enlarged stimulus sets since subsequent memory effects could crucially depend on whether the social scenes evoke fear or anger. In fact, it has been argued that OXT increases social approach, including negative approach-related social emotions such as anger, while social withdrawal is inhibited (Kemp and Guastella 2011). Forth, the effects of OXT may critically depend on moderators additional to the individual characteristics controlled in our study (Bartz et al. 2011). For example, recent studies have found that oxytocinergic effects depend on attachment style (Kiss et al. 2011), individual variability in trait anxiety (Alvares et al. 2012) and experiences of childhood trauma (Bakermans-Kranenburg et al. 2012). In addition, contextual factors (Alvares et al. 2010; De Dreu 2012b) as well as genetic predisposition (Tost et al. 2010) can influence OXT-induced effects. Finally, the present study would have benefited from the inclusion of subjective arousal ratings and physiological measures of arousal such as skin conductance to clarify the potential explanation of diminished arousal levels after OXT application.

5.6 Conclusion

In conclusion, the present study provides first evidence of memory effects of OXT administered prior to both encoding and retrieval of emotional pictures. We demonstrated that repeated OXT application significantly improved memory certainty for negative social stimuli. This promnestic effect of OXT interacted with emotion regulation when participants had been instructed to increase their negative emotions during encoding. Our findings indicate that OXT potentially enhances the perception of aversive aspects in social situations, which might be mediated by reduced amygdala and facilitated insular responses. Future neuroimaging studies are needed, though, in order to specify the effects of OXT on recognition memory and its underlying neural mechanisms.

6 General Discussion

There has been a lot of controversy in research investigating emotional memories (Kensinger 2009). As described in the preceding chapters, the effects of emotion on memory depend on many factors such as the characteristics of emotional stimuli (e.g. valence and arousal level, approach- vs. withdrawal-related emotion), the type of memory system (e.g. working memory, episodic memory), and individual differences (e.g. mood, personality). Importantly, studies examining emotion-memory interactions at a neural level moved beyond separating emotional and cognitive brain areas and suggested their integration in cortical regions with a high degree of connectivity (Gray et al. 2002; Pessoa 2008). A variety of methods can be used to assess emotional memories. This thesis used a multimodal approach by including neuroimaging, non-invasive brain stimulation and the application of intranasal OXT, providing a greater understanding of neural and cognitive mechanisms underlying emotional memories.

6.1 Integration of findings

The primary aim of this thesis was to investigate the influence of emotional content on working memory in healthy participants, at both the neural and behavioral level. In three consecutive studies, we employed variations of the EMOBACK task which provides a novel means of studying the interface between working memory and emotion. By including carefully matched emotional words from the BAWL-R (Võ et al. 2009) and the DENN-BAWL (Briesemeister et al. 2011b) in a working memory n-back task, we were able to investigate valence and arousal effects as well as the impact of distinct emotion processing. The experimental approaches used in our studies on emotional working memory included fMRI, rTMS and tDCS. The application of non-invasive brain stimulation techniques allowed us to further explore models of hemispheric lateralization in emotion processing and the causal role of the DLPFC.

In the first study (Chapter 2), participants were presented with a 2-back version of the EMOBACK task including positive, negative and neutral words. Stimuli were nouns matched according to arousal levels in order to elucidate both valence and arousal

effects. Using fMRI, it was shown that the EMOBACK task activated the bilateral DLPFC and dACC, but deactivated cortical midline regions. In line with our results, activity in the dACC has often been described in relation to increased cognitive effort or attention (Botvinick et al. 2004; Duncan and Owen 2000) and cortical midline regions as a part of the default-mode network (Raichle and Gusnard 2005; Raichle et al. 2011) are characterized by deactivations during emotional-cognitive tasks (Grimm et al. 2009; Gusnard et al. 2001; Northoff et al. 2004). Our findings regarding bilateral DLPFC activation are in accordance with numerous previous studies demonstrating that the DLPFC is implicated in working memory (e.g. Goldman-Rakic 1994; Jonides et al. 1993). With regard to the impact of emotional content, we further demonstrated that both positive and negative words yielded higher signal increases in the bilateral DLPFC as compared to neutral words. This may reflect higher cognitive effort due to interference with emotion. Indeed, it has been demonstrated that more DLPFC activity is necessary to maintain performance under task-irrelevant emotional stimuli (Neta and Whalen 2011). Another potential explanation is a general arousal effect, which is supported by our data revealing a parametric modulation of DLPFC activity by individual arousal ratings of our participants. Interestingly, also with regard to our subsequent brain stimulation studies (Chapters 3 and 4), we found a stronger recruitment of the left DLPFC during positive and right DLPFC during negative stimuli, supporting the valence hypothesis of lateralized emotion processing (Davidson and Irwin 1999). At the behavioral level, the findings of our first study showed no influence of emotional content on task accuracy; however, we cannot exclude the possibility that findings might be confounded due to a ceiling effect in the 2-back version of the EMOBACK task. Nevertheless, we further showed decreased reaction times for negative words, which are possibly more sensitive to small modulations by emotional content. This may indicate a detrimental effect of negative emotional content, as shown in previous studies (Kensinger and Corkin 2003; Becerril and Barch 2010).

In the second study (Chapter 3), we aimed to investigate the causal role of the prefrontal cortex in emotional working memory by using rTMS. Based on our previous fMRI data (Chapter 2), low-frequency rTMS (1Hz, 15min, 110% of the resting motor threshold) was applied over the left or right DLPFC prior to EMOBACK task performance. We presented a 3-back version of the EMOBACK task in order to avoid ceiling effects. In a sham-controlled crossover design, stimulation effects were

analyzed by differences in task performance in comparison to baseline measurements. In order to further explore hemispheric lateralization of emotion processing, selected EMOBACK stimuli were words assigned to the distinct emotion categories fear and anger taken from the DENN-BAWL (Briesemeister et al. 2011b). Words were matched for valence and arousal as well as with regard to lexical and sublexical dimensions. Based on numerous findings suggesting that anger is associated with approach motivation, anger-related stimuli allow the disentangling of positive emotional valence from approach motivational direction (Harmon-Jones 2004; Harmon-Jones et al. 2010). In line with this model, our rTMS study revealed lateralized stimulation effects for fear-related words, indicating that negative withdrawal-related emotions are associated with the right DLPFC. More specifically, working memory performance for fear-related words was found to be improved after stimulating the right DLPFC and impaired after stimulating the left DLPFC. A potential explanation might be seen in the stimulation-induced inhibition of the right DLPFC, which may have reduced the attentional bias towards fear-related words, resulting in enhanced working memory task performance through a prioritized processing of task-relevant information. In contrast, the contralateral activation of the right DLPFC might have enhanced the attentional bias towards fear-related words, resulting in impaired working memory task performance through a diminished ability to suppress task-irrelevant emotional information. This hypothesis is supported by previous findings indicating that low-frequency rTMS over the right DLPFC reduces vigilant attention to fear-related stimuli (van Honk et al. 2002). Furthermore, we did not find evidence of left-hemisphere dominance for processing anger-related words as demonstrated in previous research (d'Alfonso et al. 2000; Harmon-Jones 2003). Our data, however, indicated that anger- and fear-related words are differentially processed, providing support for a dissociation of negative withdrawal- and approach-related emotions according to the motivational direction model (Harmon-Jones 2004; Harmon-Jones et al. 2010). Therefore, this study extended our previous fMRI findings demonstrating a stronger recruitment of the right DLPFC during negative words (Chapter 2) by disentangling negative approach-related from negative withdrawal-related emotions.

In the third study (Chapter 4), we further extended the investigation of the causal role of the DLPFC in emotional working memory by additionally considering state-dependent effects of rTMS. A growing body of research has demonstrated that the preactivation of the targeted cortical region can strongly influence stimulation effects

(for a review, see Silvanto et al. 2008). Therefore, we used tDCS priming to modulate the neural activation state prior to low-frequency rTMS applied over the right DLPFC. Each participant received anodal and cathodal tDCS followed by either active or sham rTMS prior to EMOBACK task performance. In line with our previous rTMS study (Chapter 3), selected stimuli were words assigned to the distinct emotion categories fear and anger taken from the DENN-BAWL (Briesemeister et al. 2011b). Words were again carefully matched for valence and arousal as well as with regard to lexical and sublexical dimensions. Our findings revealed that the withdrawal-related emotion fear is associated with the right DLPFC and seems to be differentially processed as compared to the approach-related emotion anger. These findings replicate the findings of our previous rTMS study (Chapter 3), providing further support of a frontal asymmetry of emotion processing as proposed by the motivational direction model (Harmon-Jones 2004; Harmon-Jones et al. 2010). No general state-dependent effects of prefrontal rTMS on working memory were found.

In contrast to our previous studies (Chapters 2 and 3), our tDCS-rTMS study (Chapter 4) revealed a detrimental effect of negative emotional content on working memory performance in terms of impaired task accuracy independent of stimulation. In our fMRI study (Chapter 2), however, participants responded generally slower to negative words in a less difficult 2-back version of the EMOBACK task, suggesting that negative emotional content might impair working memory task performance. It has been argued that emotionally salient stimuli capture and hold attention, resulting in increased task demands for higher executive functions such as working memory (Lindström and Bohlin 2012). Our behavioral findings of a detrimental effect of negative emotional content in terms of slower reaction times (Chapter 2) and decreased task accuracy (Chapter 4) support previous studies demonstrating that task-irrelevant, negative emotional content might impair task performance by drawing processing resources away from the actual task (Becerril and Barch 2010; Kensinger and Corkin 2003; Lindström and Bohlin 2012; Perlstein et al. 2002).

Furthermore, we explored the potential of OXT in enhancing emotional recognition memory and the interaction with emotion regulation during encoding (Chapter 5). Conflicting findings of previous research demonstrated both memory-enhancing (Guastella et al. 2008; Rimmele et al. 2009; Savaskan et al. 2008) and memory-impairing oxytocinergic effects (Herzmann et al. 2012). In a double-blind placebo-

controlled design, we investigated the influence of a single (prior to encoding) and a repeated (prior to encoding and retrieval) intranasal administration of OXT on recognition memory for emotional pictures taken from the IAPS (Lang et al. 2008). Participants performed an emotion regulation task followed by a surprising recognition memory task. Our results indicated that repeated OXT administration significantly improved memory certainty for negative social stimuli. Regarding the influence of emotion regulation, the promnestic effect of OXT was more pronounced when participants had been instructed to increase their negative emotions during encoding. Our findings indicate that OXT facilitates the processing of negative social stimuli during memory encoding and retrieval, possibly by enhancing the perception of aversive aspects in social situations, which might be mediated by reduced amygdala (Domes et al. 2007; Kirsch et al. 2005; Riem et al. 2011) and facilitated insular responses (Striepens et al. 2012).

In conclusion, different experimental approaches were used in this thesis to study the neural and cognitive mechanisms underlying emotional memories. Our findings suggest that the impact of emotional content on memory depends on stimulus and task characteristics. With regard to emotional working memory, our behavioral data indicated a detrimental effect of negative emotional content on working memory performance. A potential explanation might be seen in an attentional bias away from the actual working memory task to task-irrelevant emotion processing. At a neural level, our neuroimaging as well as brain stimulation findings support a crucial role of the DLPFC in emotional working memory and indicated hemispheric brain lateralization in emotion processing. With regard to recognition memory, we found memory-enhancing oxytocinergic effects in processing negative social stimuli when OXT was applied prior to both encoding and retrieval.

6.2 Perspectives

Based on our previous research on prefrontal stimulation effects on emotional working memory, we aimed to further explore state-dependent rTMS effects by additionally including light exposure in a subsequent rTMS study. Interestingly, blue relative to green light has been shown to increase brain responses to emotional stimuli in healthy individuals (Price and Drevets 2010; Vandewalle et al. 2011).

Participants performed a 3-back version of the EMOBACK task with words classified as positive, negative and neutral according to the BAWL-R (Võ et al. 2009). We used light exposure presented via video goggles 5min prior to and during rTMS application (1Hz, 15min, 110% of the resting motor threshold) applied over the right DLPFC. In a randomized sham-controlled within-subjects design, 30 healthy young participants received neuronavigated, MRI-based rTMS combined with blue and green light exposure before task performance (Fig. 18).

Fig 18. Schematic illustration of the rTMS study using light exposure (blue and green) prior and during rTMS application (active and sham).

Accuracy and reaction times of correct responses in the emotional working memory task were recorded at baseline and after treatment. Over the course of the study, the emotional state of the participants was assessed with a Multidimensional Mood Questionnaire (MDBF; Steyer et al. 1997).

Our first results revealed that active rTMS combined with blue light exposure significantly improved task performance in the emotional working memory task. Remarkably, this effect could be attributed to words with positive emotional values, indicating valence-specific brain lateralization in emotional processing. These findings further illustrate the importance of controlling potential state-dependent effects in studies using brain stimulation.

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Eidesstattliche Erklärung

Hiermit versichere ich, dass ich die vorliegende Arbeit selbständig und nur unter Verwendung der angegebenen Quellen und Hilfsmittel erarbeitet und verfasst habe. Diese Arbeit hat keiner anderen Prüfungsbehörde vorgelegen.

Berlin, den 20.03.2013

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