**Fachbereich Erziehungswissenschaft und Psychologie der Freien Universität Berlin**

# Modulating Social Cognition:

## Effectiveness of Oxytocin Application and Transcranial Direct Current Stimulation

**Kumulative Dissertation**

**Zur Erlangung des akademischen Grades**

**Doktorin der Philosophie (Dr. phil.)**

**Vorgelegt von**

**Dipl.-Psych.**

**Melanie Feeser**

**Berlin, 2015**

**Erstgutachter:**

**Prof. Dr. Malek Bajbouj**

**Zweitgutachter:**

**Prof. Dr. Hauke Heekeren**

**Tag der Disputation:**

**04.11.2014**

**Meinen Eltern Maya und Mecki gewidmet**

# Danksagung

Ich möchte mich an dieser Stelle bei allen Personen bedanken, die mir bei der Entstehung dieser Arbeit mit Rat und Tat zur Seite gestanden sind. Hier gilt mein Dank an erster Stelle Prof. Malek Bajbouj für seine Betreuung und die ermutigende Unterstützung während der gesamten Zeit. Ich bin sehr dankbar für sein Vertrauen in meine Arbeit und die Freiheit, die er mir ermöglicht hat, meine eigenen Forschungsinteressen auszubilden und zu verfolgen. Prof. Hauke Heekeren danke ich für sein Interesse und die Bereitschaft, meine Arbeit als Zweitgutachter zu betreuen.

Zudem möchte ich mich ganz herzlich bei allen Kolleginnen und Kollegen meiner Arbeitsgruppe bedanken für ihre Unterstützung, die großartige Arbeitsatmosphäre und alle Freundschaften, die daraus in den letzten Jahren entstanden sind. Ich denke gerne an die Stunden zurück, die wir mit diversen sportlichen, kulinarischen und musikalischen Aktivitäten ausgefüllt haben. Ohne euch hätte alles nur halb so viel Spaß gemacht!

Besonderer Dank geht an Simone für ihre unermüdliche Hilfe bei der Auswertung meiner Daten, der Korrektur meiner Manuskripte sowie der Planung der Experimente. Durch ihre intensive Unterstützung und Zuversicht in meine Arbeit hat sie einen großen Anteil am Gelingen dieser Dissertation. Ebenfalls danken möchte ich Kristin, die mir besonders zu Beginn wesentlich geholfen hat, meine inhaltlichen und methodischen Kenntnisse auszubauen und mich immer wieder motiviert hat.

Yan, Philipp und Matti haben mich mit ihren Programmierkenntnissen und technischen Skills stets tatkräftig unterstützt, wenn Hilfe dringend nötig war. Vielen Dank dafür. Ganz herzlich möchte ich mich auch bei Anne und Sabine bedanken für den emotionalen und fachlichen Beistand während der letzten Jahre.

Für die anregenden interdisziplinären Diskussionen geht mein Dank an die Kolleginnen und Kollegen meiner Graduiertenschule “Languages of Emotion”. Adam und Judith danke ich herzlich für ihre unersetzbare Hilfe bei methodischen und inhaltlichen Fragen sowie bei der Korrektur der Arbeit. Und natürlich dafür, dass sie als gute Freunde immer ein offenes Ohr für mich haben.

Ich widme diese Arbeit meinen Eltern, die mich in allen Phasen meines Lebens liebevoll unterstützt und gefördert haben und meinen beruflicher und persönlichen Werdegang damit so entscheidend geprägt haben. Danke von ganzem Herzen.

Ein ganz besonderer Dank gilt Sven, der seit Beginn meiner Dissertation geduldig Höhen und Tiefen mit mir durchlebt und mich immer wieder auffängt und ermutigt. Er gibt mir die Zuversicht, dass wir zusammen alle Hindernisse bewältigen können.

# Table of Content

**ENGLISH SUMMARY**

**DEUTSCHE ZUSAMMENFASSUNG**

**1 GENERAL INTRODUCTION ..... 1**

**1.1 Social Cognition ..... 1**
1.1.1 Emotion Recognition ..... 1
1.1.2 Mentalizing ..... 2
1.1.3 Emotion Regulation ..... 3

**1.2. Social Cognition in mental disorders ..... 4**

**1.3 Modulating Social Cognition ..... 6**
1.3.1 The neuropeptide Oxytocin ..... 7
1.3.1.1 Variability of oxytocinergic effects ..... 10
1.3.2 The noninvasive brain stimulation technique tDCS ..... 11

**1.4 Aims of research ..... 12**

**2 THE BENEFICIAL EFFECT OF OXYTOCIN ON AVOIDANCE-RELATED FACIAL EMOTION RECOGNITION DEPENDS ON EARLY LIFE STRESS EXPERIENCE ..... 14**

**2.1 Introduction ..... 15**

**2.2 Methods ..... 18**
2.2.1 Subjects ..... 18
2.2.2 Experimental design ..... 19
2.2.3 Emotion Recognition task ..... 19
2.2.4 Control variables ..... 20
2.2.5 Statistical analysis ..... 21

**2.3 Results ..... 21**
2.3.1 Demographics and individual characteristics ..... 21
2.3.2 Accuracy ..... 23

**2.4 Discussion ..... 25**

**3 OXYTOCIN IMPROVES MENTALIZING – PRONOUNCED EFFECTS FOR INDIVIDUALS WITH ATTENUATED ABILITY TO EMPATHIZE ..... 30**

**3.1 Introduction ..... 31**

**3.2 Methods ..... 34**
3.2.1 Subjects ..... 34
3.2.2 Experimental design ..... 34
3.2.3 Reading the Mind in the Eye task (RMET) ..... 35
3.2.4 Control variables ..... 36
3.2.5 Statistical analysis ..... 36

**3.3 Results ..... 37**
3.3.1 Demographics and individual characteristics ..... 37
3.3.2 Accuracy ..... 38

**3.4 Discussion** ..... **40**

**3.5 Conclusion** ..... **43**

**4 TRANSCRANIAL DIRECT CURRENT STIMULATION ENHANCES COGNITIVE CONTROL DURING EMOTION REGULATION** ..... **44**

**4.1 Introduction** ..... **45**

**4.2 Methods and material** ..... **49**
4.2.1 Subjects ..... 49
4.2.2 Experimental design ..... 49
4.2.3 Reappraisal task ..... 50
4.2.4 Stimuli and trial structure ..... 50
4.2.5 Control variables ..... 52
4.2.6 Transcranial direct current stimulation ..... 52
4.2.7 Recording and analysis of Skin Conductance and Eye Tracking data ..... 52
4.2.8 Statistical analysis ..... 53

**4.3 Results** ..... **54**
4.3.1 Demographics and individual characteristics ..... 54
4.3.2 Effects of tDCS on emotional ratings ..... 55
4.3.3 Effects of tDCS on SCR ..... 56
4.3.4 Differences in gaze fixation ..... 58

**4.4 Discussion** ..... **58**

**4.5 Limitations** ..... **62**

**4.6 Conclusion** ..... **63**

**5 GENERAL DISCUSSION** ..... **64**

**5.1 Integration of findings** ..... **64**

**5.2 Perspectives** ..... **72**

**6 REFERENCES** ..... **75**

**7 EIDESSTATTLICHE ERKLÄRUNG** ..... **94**

**8 CURRICULUM VITAE** ..... **95**

**9 LIST OF PUBLICATIONS** ..... **98**

**9.1 First author publications** ..... **98**

**9.2 Co-author publications** ..... **98**

**10 CONFERENCE POSTER PRESENTATIONS** ..... **100**

**11 CONFERENCE TALKS** ..... **100**

## English Summary

The overall aim of this dissertation was to evaluate different methods of facilitating core social cognitive functions. Previous studies have provided evidence for beneficial effects of both intranasal oxytocin (OXT) application and transcranial direct current stimulation (tDCS) in modulating social cognition. However, it has also been demonstrated that the degree to which individuals are susceptible to OXT varies substantially. For example, the response depends on environmental factors and socio-emotional abilities. Hence, the present dissertation additionally aimed to further identify individual differences in participants regarding their benefit from OXT application.

In study 1, we therefore used a pharmacological approach to investigate the effects of OXT on the recognition of basic facial expressions. To account for the role of environmental factors in the modulation of central sensitivity to the effects of OXT, we investigated whether these depend on early life stress (ELS) experience. Our results show that OXT improved emotion recognition for avoidance-related emotions (for example fear and sadness). This effect was more pronounced in participants with lower levels of ELS experience. These findings are compatible with previous studies reporting that OXT modulates motivational behavior. In addition, our data suggest that ELS experience might have an impact on the development of the central nervous OXT system which in turn leads to lower sensitivity to the effects of intranasal OXT administration.

In study 2, we investigated the ability to infer complex mental states of others. Additionally, we evaluated whether the effects of OXT depend on the ability to empathize. Our results indicate that OXT specifically enhanced mentalizing accuracy for difficult items in participants with lower empathy scores. Our findings corroborate previous studies which showed that OXT induced effects are more pronounced in individuals with lower socio-emotional skills.

In study 3, we investigated a more elaborate social cognitive process, namely cognitive reappraisal. A number of studies have consistently demonstrated that the dorsolateral prefrontal cortex (dlPFC) plays a critical role in cognitive reappraisal. We therefore applied tDCS, which has been shown to effectively modulate dlPFC activation, to investigate effects of increased dlPFC excitability on up- and downregulation of negative emotions. Changes in reappraisal success were indexed by subjective emotional arousal

ratings and skin conductance responses. Our results demonstrate that tDCS increased cognitive reappraisal capacities in both directions by either increasing or decreasing emotional responsiveness. By showing a relationship between prefrontal tDCS and reappraisal success our results may open up new possibilities for the use of tDCS as an add-on treatment in patients with impairments in emotion regulation.

To summarize, the present studies confirm that OXT application can be effectively used to facilitate not only the recognition of basic emotional expressions, but also the inference of mental states of others, which represents a more complex social cognitive function. In addition, our results highlight the importance of considering environmental factors and socio-emotional skills when examining oxytocinergic effects on social cognition. Results from study 3 show for the first time that prefrontal tDCS can effectively facilitate cognitive reappraisal.

Furthermore, possible implications for OXT in the treatment of mental disorders, which are characterized by derogations in core social cognitive domains, are being discussed.
The last chapter includes preliminary results of an additional functional magnetic resonance imaging (fMRI) study about the effects of OXT on selective attention. The aim of this study was to identify possible explanatory mechanisms underlying the OXT effects on social cognition.

## Deutsche Zusammenfassung

Das übergeordnete Ziel der vorliegenden Arbeit lag in der Evaluation verschiedener Methoden zur Verbesserung sozial-kognitiver Funktionen. Bisherige Studien deuten darauf hin, dass soziale Kognition durch die intranasale Applikation von Oxytocin (OXT) und transkranielle Gleichstromstimulation (tDCS) moduliert werden kann. Jedoch zeigte sich in diesen Studien auch eine erhebliche intraindividuelle Variabilität hinsichtlich der Oxytocinsensitivität, d.h. hinsichtlich des Ausmaßes, in dem behaviorale und neuronale Parameter durch OXT moduliert werden. Da die Oxytocinsensitivität durch Umweltfaktoren und sozial-emotionale Kompetenzen entscheidend beeinflusst zu sein scheint, lag ein Fokus dieser Arbeit auf der Untersuchung der Effekte dieser Variablen.

In der ersten Studie wurde untersucht, wie Oxytocin die Fähigkeit zum Erkennen des mimischen Ausdrucks von Basisemotionen in Abhängigkeit von frühkindlichen Stresserfahrungen moduliert. Die Ergebnisse zeigen, dass Oxytocin das Erkennen von Emotionen verbessert, die mit Vermeidungsverhalten assoziiert sind (wie z.B. Angst und Traurigkeit). Dieser Effekt war besonders ausgeprägt bei Versuchspersonen, die keine oder wenige frühkindliche Stresserfahrungen aufwiesen. Die Ergebnisse stehen im Einklang mit früheren Studien, die einen differentiellen Oxytocineffekt auf motivationales Verhalten zeigen konnten. Darüber hinaus unterstreichen die Resultate den Einfluss frühkindlicher Stresserfahrungen auf die Entwicklung des Zentralnervensystems und die damit einhergehende verminderte Oxytocinsensitivität.

In der zweiten Studie wurde die Mentalisierungsfähigkeit anhand einer Aufgabe zum Erkennen komplexer mentale Zustände in mimischen Ausdrücken untersucht. Zusätzlich sollte untersucht werden, inwieweit die Effekte der Oxytocin-Applikation auf die Mentalisierungsfähigkeit von der individuellen Empathiefähigkeit abhängen. Die Ergebnisse zeigen eine durch Oxytocin verbesserte Mentalisierungsfähigkeit, insbesondere bei Probanden mit geringer Empathiefähigkeit. Diese Ergebnisse bestätigen frühere Studien, die ausgeprägtere Oxytocin- Effekte bei Probanden mit niedrigen sozial-emotionalen Kompetenzen nachweisen.

In der dritten Studie wurde mit dem kognitiven Reappraisal (Neu- oder Umbewertung) ein komplexerer sozial-kognitiver Prozess untersucht. Eine Anzahl von Studien weisen darauf hin, dass der dorsolaterale präfrontale Cortex (dlPFC) eine entscheidende Rolle

im Reappraisalprozess spielt. Frühere Untersuchungen konnten zeigen, dass neuronale Aktivität im dlPFC durch tDCS moduliert werden kann. In der vorliegenden Studie wurde daher tDCS angewendet, um der Frage nachzugehen, wie sich eine erhöhte Aktivierung im dlPFC auf das Hoch – oder Runterregulieren negativer Emotionen auswirkt. Die Effektivität des Reappraisal wurde anhand von Veränderungen in der subjektiven Beurteilung der emotionalen Erregung, sowie der Hautleitfähigkeit gemessen. Die Ergebnisse sprechen dafür, dass durch tDCS Emotionsregulation in beide Richtungen verbessert wurde. Dies zeigte sich in einer jeweils intensivierten oder reduzierten negativen Bewertung von Emotionen und bildete sich zusätzlich in einer erhöhten oder verminderten Hautleitfähigkeit ab. Die vorliegende Arbeit beschreibt somit einen Zusammenhang zwischen durch tDCS modulierter Aktivität des präfrontalen Cortex und der Fähigkeit zur Emotionsregulation. Die Ergebnisse weisen auf eine mögliche Nutzung von tDCS als Augmentationsbehandlung bei Patienten mit eingeschränkter Fähigkeit zur Emotionsregulation hin.

Insgesamt unterstützen die vorliegenden Ergebnisse den förderlichen Einfluss von Oxytocin auf Fähigkeiten zur Emotionserkennung und Mentalisierung. Darüber hinaus zeigen die Befunde jedoch auch, wie wichtig es ist, Umweltfaktoren und sozial-emotionale Kompetenzen zu berücksichtigen, da diese die Oxytocineffekte ganz entscheidend modulieren. Zusätzlich konnte erstmals gezeigt werden, dass durch tDCS eine Verbesserung der Reappraisal-Fähigkeit erreicht werden kann.

Die klinische Relevanz der Befunde im Hinblick auf Behandlungsmöglichkeiten von psychischen Störungen, bei denen verminderte sozial-kognitive Funktionen im Vordergrund stehen, wird in der vorliegenden Arbeit ebenfalls diskutiert. Das letzte Kapitel dieser Arbeit beschreibt die vorläufigen Ergebnisse einer Studie, in der die Rolle der selektiven Aufmerksamkeit bei der Modulation von Oxytocineffekten auf soziale Kognition mittels funktioneller Magnetresonanztomographie (fMRT) untersucht wurde.

# 1 General Introduction

## 1.1 Social Cognition

Social cognition is a multidimensional psychological construct, which consists of several processes that allow individuals to decode and encode the social world (Beer and Ochsner 2006). According to Lieberman (2007a), core processes of social cognition involve the understanding of oneself, the understanding of others and the control of oneself. With the help of these processes, individuals are able to interact with each another and share intentions and experiences, which is crucial for functioning in a social environment (Frith 2008; Frith and Frith 2012). Hence, several studies on social cognition highlight evolutionary concerns as the motivation for understanding the desires, goals and intentions of others (Cosmides and Tooby 2004).

An important aspect of social cognition is the exchange of social signals. This is one of the first steps in navigating the social world and usually includes the processing of nonverbal cues with socio-emotional meaning. By sending and receiving social cues, we are able to communicate our mental state and read those of others. Especially non-verbal information from the face conveys a rich source of social information (Blair 2003). The present dissertation focuses on core components of social cognition that play an important role in understanding others, such as the ability to recognize basic facial emotional expressions and the identification of more complex mental states from facial cues. Furthermore, a more differentiated process, namely the ability to control oneself using cognitive reappraisal strategies is investigated.

### 1.1.1 Emotion Recognition

As mentioned above, a core process of social cognition is the ability to understand others. This ability can be investigated at a basic level by examining the capacity to recognize facial emotional expressions. The human face is equipped with a complex muscle structure that is claimed to exist primarily for the purpose of communicating with others (Huber 1931). Empirically it has been shown that humans are able to quickly and accurately decode basic emotional expressions (Ekman and Friesen 1971) from facial cues. The recognition of facial emotional expressions has been the focus of a large number of psychological studies over the past decades (Adolphs et al. 2002; Bassili 1979; Mothersill et al. 2014). In these studies, emotion recognition usually refers to an

individual's ability to accurately detect emotional states from photographs depicting basic emotional expressions.

A review by Adolphs (2002) suggests the following processes to be involved in recognizing emotions from faces: First, emotion recognition can be understood as part of a basic perception process. Empirically it has been shown that humans are capable of identifying facial emotions simply on the basis of geometric visual properties of a stimulus (Calder et al. 2001). Hence, on the basis of perceptual processing, humans can create a category structure of emotions that is equal with the semantic structure of the emotion concept (Adolphs 2002). Second, one might also hypothesize that emotion recognition involves the generation of associated knowledge (Damasio and Damasio 1994). That is, during an emotional facial recogniton task, participants need to recall previously stored memories of other persons´ facial expressions that they once perceived and match them to the stimuli presented.

Previous research demonstrates that facial emotion recognition is a complex process that implicates a network of interconnected brain regions. Specifically, it has been shown that this network includes the occipital, temporal and orbitofrontal cortices, the basal ganglia, the amygdala and right parietal cortices (Adolphs 2002).

### 1.1.2 Mentalizing

Beyond solely recognizing basic emotional facial expressions of others, humans also have the ability to understand and predict more complex causes of other peoples' behavior. During social interactions, humans need to perceive, represent and reason about the intentions of one's self and others. This capacity is referred to as mentalizing (Frith and Frith 2006a; 2006b). Mentalizing is an important prerequisite of participating in a social environment and implies the ability to interpret information from multiple sources, such as knowledge about the other person's perspective and beliefs, as well as non-verbal cues such as facial expressions and gaze direction (Baron-Cohen 1995). According to Frith and Frith (2006a) there are two types of mental states that can affect the way we interact with others. We can identify long-term dispositions, for example if others can be seen as trustworthy or deceitful, as well as short-term dispositions, such as happiness or fear. The foundation for mentalizing is partly rooted in infant-caregiving

attachment relationships and matures over the lifespan with increased interpersonal interactions (Fonagy et al. 2007).

Several studies have shown a strong relationship between mentalizing and empathy (Besel and Yuille 2010; Martin et al. 1996). Findings from neuroimaging studies suggest that greater neural activity in brain circuits underlying mentalizing is related to more self-reported empathy (Hooker et al. 2008; Hooker et al. 2013). Even though mentalizing and empathy are often used as synonyms, they represent different skills that rely on distinct neuronal circuitries (Singer 2006). Over the last years a number of studies have been conducted on the neural basis of mentalizing. In these studies participants are usually requested to accurately label the mental state of others from viewing static photographs, morphed images, cartoon pictures or short videos. It has consistently been shown that the medial prefrontal cortex (mPFC), the posterior cingulate and the temporoparietal junction (TPJ) are engaged in mentalizing processes (Frith and Frith 2006a; Saxe et al. 2004; Saxe and Wexler 2005).

### 1.1.3 Emotion Regulation

Although humans are quickly able to process mental states of others, the socio-emotional significance of these mental states is not fixed. It rather strongly depends on complex cognitive reappraisal processes (Ochsner 2004). For example, another person expressing fear can evoke the motivation to help or the feeling of indifference, either depending on the way one appraises the person's intentions. Using cognitive reappraisal strategies enables us to regulate and control our thinking about the mental states of others, which in turn impacts our subsequent behavior (Ochsner and Gross 2005).
Cognitive reappraisal is an important component of emotion regulation processes and refers to changing the way one appraises a situation in order to change its emotional impact. According to Thompson (1994) emotion regulation can be defined as: "extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features, to accomplish one's goals" (p. 28). In studies investigating emotion regulation, subjects are typically trained with cognitive reappraisal strategies to down- or upregulate negative emotions elicited by pictures or videos. Ochsner et al. (2012) recently proposed a model of cognitive control processes underlying emotion regulation (see Fig. 1).

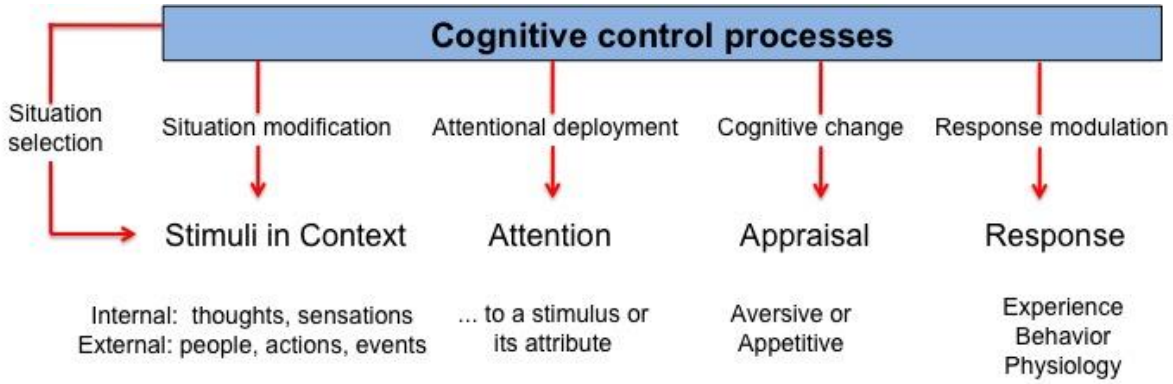


**Fig. 1** Model of the cognitive control of emotions (adapted from Ochsner et al. 2012)

Previous studies have identified a network of interconnected brain regions that are engaged while attempting to reappraise negative emotions. This network consists of the dorsolateral prefrontal cortex (dlPFC), dorsal anterior cingulate cortex (dACC), ventromedial prefrontal cortex (vmPFC), amygdala, insula and ventral striatum (Ochnser et al. 2012). Specifically, it has consistently been shown that the dlPFC plays a crucial role in this process. For example, Eippert et al. (2007) and Ochsner et al. (2004) found that both down- and upregulation of negative pictures activated the dlPFC as compared to a control condition. Prior imaging studies have shown that increased dlPFC activation is associated with altered amygdala activation during cognitive reappraisal. This results in decreased amygdala activity during downregulation and increased activation during upregulation of negative emotions (Ochsner et al. 2004).

### 1.2. Social Cognition in mental disorders

A number of studies have demonstrated that impairments in the previously described social cognitive functions are characteristic for various severe mental disorders (for a review see Hoertnagl and Hofer 2014). Recent findings in clinical samples also suggest that dysfunctions in social cognition can negatively impact quality of life, social relationships, or employment status (Fett et al. 2011; Fulford et al. 2014). In this chapter, derogations in core social cognitive functions are exemplified in major depressive disorder (MDD) and autism spectrum disorder (ASD).

Impairments in social cognition such as reduced ability to cognitively control emotions have been consistently shown in MDD (for a review see Berking and Wupperman 2012). With regard to behavioral measures, Beauregard and colleagues have demonstrated that patients with MDD report more difficulties in the downregulation of negative emotions as compared to controls (Beauregard et al. 2006). Erk and colleagues reported a reduction in emotion regulation capacities as a function of increased depressive symptom severity (Erk et al. 2010).

As mentioned earlier, neuroimaging studies in healthy participants have characterized a corticolimbic circuit involved in the top-down regulation of subcortical activation. Stronger recruitment of the dlPFC and decreased amygdala activation have been observed when participants reappraise negative stimuli as less negative (Ochsner et al. 2004). However, neuroimaging studies in patients with MDD have consistently reported hypoactivation in prefrontal brain regions (Davidson et al. 2003a; Mayberg et al. 1997; Phillips et al. 2003). In line with this, it has been shown that dysfunctional emotion regulation capacities are associated with abnormally reduced activity in lateral prefrontal cortices in MDD (for a recent review see Rive et al. 2013). Johnstone et al. (2007) propose that the lack of engagement of the lateral-ventromedial prefrontal circuitry, which is crucial for the downregulation of amygdala responses to emotional salient stimuli, plays an important role in the pathophysiology of MDD. In remitted patients with previous episodes of MDD, deficits in downregulation of amygdala responses during reappraisal have been shown by Kanske et al. (2012). The authors suggest that altered emotion regulation might be a trait-marker for MDD. Besides impairments in emotion regulation, patients with MDD also show emotion recognition deficits that are mainly characterized by a bias towards the recognition of negative emotions. That is, patients with MDD tend not to recognize happy faces correctly and recognize neutral faces as sad faces (Leppänen et al. 2004).

Impairments in social cognitive functions are also found to be key symptoms of ASD. Previous studies have shown that patients with ASD have particular difficulties in facial emotion recognition (for a review see Harms et al. 2010). The studies reviewed by Harms et al. (2010) provide evidence that participants with ASD decode facial expressions differently than controls. That is, in some cases they show impairments in labeling or matching facial emotions. In other cases their performance is comparable to

controls, possibly through the use of compensatory mechanisms such as feature-based learning or verbal mediation.

Especially non-verbal information from the eyes conveys a rich source of social information that is important in recognizing facial expressions (Baron-Cohen et al. 2000). However, atypical eye contact is a diagnostic criterion for ASD (American Psychiatric Association 1994). It has been suggested that patients with ASD show atypical gaze patterns during face processing which are characterized by spending less time on faces (Phelphey et al. 2002) and focussing less on the eye region (Klin et al. 2002). Interestingly, Kliemann et al. (2010) have demonstrated that ASD is associated with enhanced avoidance of eye contact. Specifically, the ASD group displayed more frequent eye movements away from the eyes, which in turn predicted emotional recognition performance.

It has also been shown that patients with ASD have particular difficulties in understanding the beliefs and desires of others (Frith 2001; Leslie et al. 2004). Based on these findings, it has been suggested that the problems in social communication and interaction in ASD derive from severe impairments in mentalizing abilities (Baron-Cohen 1995). For example, in an eye-tracking task that measured the spontaneous ability to mentalize, Senju et al. (2009) report that participants with Asperger syndrome failed to spontaneously infer mental states of others. Kana et al. (2014) have recently provided evidence for alterations in functional brain networks underlying mentalizing in ASD. The authors report lower activation in the TPJ, inferior frontal gyrus and premotor cortex in the ASD group. Additionally, attenuated functional connectivity was observed in the ASD group between the TPJ and motor areas.

### 1.3 Modulating Social Cognition

Dysfunctional social cognition is not only a key symptom of mental disorders, but also has derogatory consequences, such as impaired well-being and interpersonal functioning in healthy subjects (Gross and John 2005; Gross and Muñoz 2006).

Considering the importance of efficient social cognitive processes for social functioning and mental health, the question arises how these processes can be improved. With the growing body of evidence about neurobiological mechanisms of social cognition, it has become possible to directly target specific brain regions that are involved. Transcranial

direct current stimulation (tDCS) is an emerging brain stimulation technique that can be used to modulate cortical excitability in specific brain regions (please see chapter 1.3.2 for further details on tDCS). However, although the dlPFC plays a crucial role for emotion regulation and recent studies indicate that tDCS can effectively modulate dlPFC activity (Keeser et al. 2011; Weber et al. 2014), no study has yet examined whether directly modulating dlPFC activity using tDCS would result in improved capacities for cognitive reappraisal. This research gap is addressed in the present dissertation by study 3.

Another means to enhance social cognition is the intranasal application of oxytocin (OXT, Meyer-Lindenberg et al. 2011). The effects of OXT on social cognitive domains such as facial emotion recognition (for a review see van Ijzendoorn et al. 2012) and mentalizing (Domes et al. 2007b) have been widely demonstrated. However, recent findings emphasize that OXT effects on social cognition strongly depend on baseline socio-cognitive abilities (for a review see Bartz et al. 2011b) and environmental factors (Kumsta et al. 2013). To further investigate who benefits most from OXT application, further research is needed to clarify the personal variability of OXT effects. The present dissertation aims to address this question by study 1 and study 2. A more detailed summary about OXT induced effects is provided in the next chapter.

### 1.3.1 The neuropeptide Oxytocin

OXT is a neuropeptide with multifaceted functions both peripherally as a hormon and centrally as a neurotransmitter (Meyer-Lindenberg et al. 2011). After the synthesis in the magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus, OXT is processed to the posterior pituitary and released into the blood stream (see Fig. 2). Peripherally, the effects of OXT are wide in range. OXT plays an important role in reproductive functions (Corona et al. 2012) and effects the regulation of uterine contractions during labor as well as milk ejection during lactation (Keverne and Kendrick 1992).

Centrally, OXT acts as a neuromodulator and affects various brain regions that are involved in human social behavior and emotional processing (Meyer-Lindenberg et al. 2011). It exerts its central effect via direct axonal connections from the parvocellular neurons of the hypothalamus to crucial brain areas including the amygdala, hippocampus, striatum, suprachiasmatic nucleus (SCN) and brainstem.

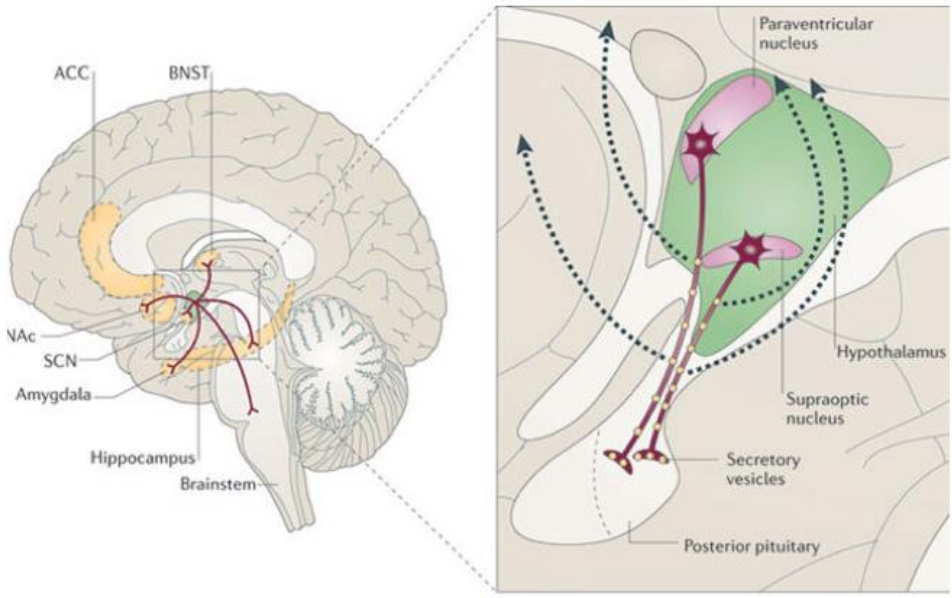


**Fig. 2** Neurophysiology of OXT (Meyer-Lindenberg et al. 2011).

The modulation of social functions using OXT application has primarily been demonstrated in animal studies. These studies have highlighted the role of OXT in social affiliative behavior, social stress and anxiety and social recognition (Bielsky and Young 2004; Carter et al. 2008; Ross and Young 2009). Following the investigations in animal models, the use of intranasal OXT in research in humans has led to the promising hypothesis that OXT is capable of modulating a wide range of complex social cognitive functions (for recent reviews, see Churchland and Winkielman 2012; Evans et al. 2014; Guastella and MacLeod 2012). Specifically, previous studies have shown that OXT promotes social approach and trust (Baumgartner et al. 2008; Feldman et al. 2007; Kosfeld et al. 2005), reduces fear and anxiety (Heinrichs et al. 2003; Kirsch et al. 2005; Petrovic et al. 2008), enhances social memory (Guastella et al. 2008b; Savaskan et al. 2008; Weigand et al. 2013) and increases emotional empathy (Hurlemann et al. 2010).

Most importantly for the present dissertation, it has been demonstrated that OXT increases the ability to mentalize (Anagnostou et al. 2012; Domes et al. 2007b; Luminet et al. 2011) as well as to correctly identify emotional facial expressions (for a review see van Ijzendoorn et al. 2012). However, studies that investigated the effect of OXT on identifying distinct facial emotions have yielded mixed results. Although it has been demonstrated that OXT promotes the identification of happy faces (DiSimplicio et al.

2009; Marsh et al. 2010; Schulze et al. 2011), other studies also showed beneficial effects on the recognition of fearful faces (Fischer-Shofty et al. 2010; Shahrestani et al. 2013). Following these inconsistent findings, it has previously been indicated that, besides its well-documented effects on enhancing the processing of emotional cues, OXT might play a more general role in modulating social motivation (Bartz and Hollander 2006). Kemp and Guastella (2011) suggest that OXT may serve to increase approach-related behaviors (i.e. emotional engagement) while inhibiting withdrawal-related behaviors (i.e. anxiety, fear). According to this hypothesis, OXT effects are not explained by modulating the processing of distinct emotions, but are rather interpreted to act on motivational behavior. However, there is only scarce evidence from studies that directly tested the effect of OXT on avoidance- and approach related cues. The present dissertation aims to fill this gap by specifically investigating approach- versus avoidance-related emotional cues in study 1 (for more information see chapter 2).

Regarding the underlying neurobiological mechanisms of OXT induced effects, the amygdala and the insula might serve as key regions (Domes et al. 2007a; Gamer et al. 2010; Striepens et al. 2012). There are several possible explanatory mechanisms for the observed effects of OXT on social cognition. First, findings by Heinrichs et al. (2003) and Kirsch et al. (2005) suggest that the effects of intranasal OXT application might be mainly interpreted as reducing anxiety. OXT dependent anxiolytic effects have been demonstrated in mice (Mantella et al. 2003; Ring et al. 2006) as well as in humans (Heinrichs et al 2003). However, studies in humans that measured mood and anxiety changes after OXT application have reported no changes (for a review see MacDonald et al 2011). Second, another hypothesis proposes that OXT drives the desire for social approach, social affiliation and attachment (for a review see Heinrichs et al. 2009; Kemp and Guastella 2011). Third, other studies suggest that OXT increases the perceptual salience processing of social cues and modulates selective attention For example, previous studies showed that OXT promotes the detection of very briefly presented emotional faces (Schulze et al. 2011) and increases gaze to the eye region (Andari et al. 2010; Guastella et al. 2008a), thus accentuating cues that are highly relevant for interpersonal communication.

#### 1.3.1.1 Variability of oxytocinergic effects

While the beneficial effects of OXT application on social cognition have been shown by a number of studies (for a review see Meyer-Lindenberg et al. 2011), there is accumulating evidence that the degree to which individuals are susceptible to OXT application is not uniform but varies substantially. Previous studies have highlighted the important role of personal variability in social endocrinology (for reviews, see Bartz et al. 2011b; Olff et al. 2013). The influence of differential socio-emotional skills on OXT effects has been previously demonstrated (Bartz et al. 2011b). It seems that the effect of OXT application is more pronounced for participants with lower socio-emotional skills. For example, Quirin et al. (2011) showed that OXT effects on stress-contingent cortisol release depend on baseline emotion regulation abilities. Specifically, subjects with low emotion regulation abilities benefit from OXT application. In line with this, Leknes and colleagues showed that differences in baseline emotional sensitivity predict the effects of OXT on the accuracy rate for hidden emotional expressions (Leknes et al. 2013). As mentioned in chapter 1.1.2, although recent studies indicate that empathy is associated with core domains of social cognition such as mentalizing (Besel and Yuille 2010; Martin et al. 1996), no study has yet examined whether the effects of OXT on mentalizing depend on the ability to empathize. This question is addressed in study 2.
In line with the above-mentioned differences in reactivity to OXT, recent studies suggest that environmental factors such as early life stress (ELS) experience also impact the effects of OXT. Specifically, it has been suggested that effects of OXT administration strongly depend on the personal family history of the participants, with lower effects in individuals with a non- supportive family background (for a review, see Bakermans-Kranenburg and Van Ijzendoorn 2013). This notion gains considerable support from studies investigating the impact of ELS experience on the oxytocinergic system (Fries et al. 2005; Heim et al. 2009). Although emotional facial recognition is crucial for social cognition, no study has yet investigated whether the effects of OXT on the ability to identify emotional faces are altered by ELS experience. Study 1 addresses this question.

Taken together, these studies highlight the importance of considering both socio-emotional skills and environmental factors when evaluating the potential of OXT in targeting social cognition.

### 1.3.2 The noninvasive brain stimulation technique tDCS

tDCS is a non-invasive brain stimulation technique that uses low amplitude direct currents to modulate the level of cortical excitability. During tDCS application, a continuous weak electrical current is applied through two sponge electrodes soaked with saline solution, which are positioned over the participant's scalp surface. It induces transient, stimulation polarity-dependent excitability shifts of the human cortex via neuronal de- or hyperpolarization (Miranda et al. 2006). Specifically, anodal tDCS results in increased cortical excitability, whereas cathodal tDCS decreases it (Nitsche and Paulus 2000). The effect of tDCS depends on specific parameters such as the orientation of the current flow relative to the stimulated neurons, the stimulation duration and the current strength in relation to the electrode size (Nitsche et al. 2007). In most of the studies using tDCS, the maximum stimulation length is set to 30 minutes at intensities of 1-2 mA (see Fig. 3 for a typical tDCS setup). The effects of tDCS application have been demonstrated to last for up to one hour after several minutes of continuous stimulation (Nitsche and Paulus 2000). Previous studies have shown that the neurophysiological mechanisms of tDCS are associated with long-term potentiation and depression (Nitsche and Paulus 2000).

Empirically it has been shown that anodal tDCS of the dlPFC is associated with working memory enhancement (Fregni et al. 2005) and improvement in other cognitive domains such as planning ability (Dockery et al. 2009) and classification learning (Kincses et al. 2004). Despite the promise of tDCS effects in enhancing cognitive functioning, less attention has been paid so far to investigate emotional processing. Recent work by Peña-Gómez et al. (2011) has proposed that tDCS over the dlPFC reduces the perceived degree of emotional valence for negative pictures. The authors explained this effect by a tDCS induced enhancement of cognitive control over emotional experience. In line with these results, Boggio et al. (2009) demonstrated that prefrontal tDCS resulted in decreased discomfort ratings during the presentation of images depicting human pain. It is important to note that these studies did not apply standardized cognitive reappraisal instructions. Therefore, their findings cannot be directly associated with the improvement of emotion regulation abilities induced by tDCS.

To summarize, tDCS is an emerging brain stimulation technique that can be used for addressing the question of causality in studies on cognition and emotion. For example, as mentioned earlier, there is substantial evidence from brain imaging studies for the

role of dlPFC in cognitive reappraisal processes (for a review see Ochsner and Gross 2005). However, these are mostly correlational and only very few studies have investigated causal mechanisms between dlPFC activation and cognitive reappraisal. Consequently, it still remains unclear whether cortical excitability enhancing anodal stimulation over the dlPFC would result in improved capacities for cognitive reappraisal.

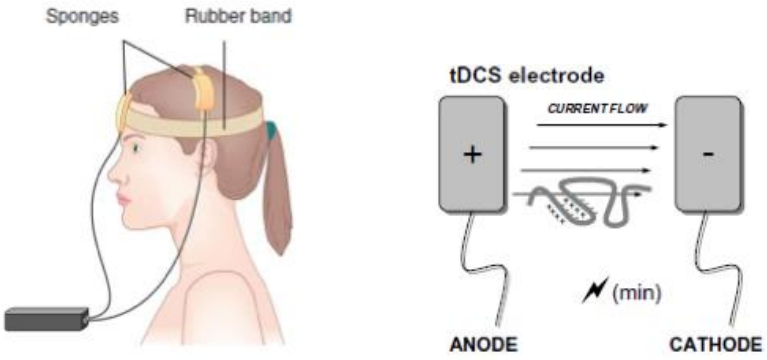


**Fig. 3** Typical tDCS setup (Rosa and Lisanby 2012). The current flows from the anode through the skull and brain to the cathode (Nitsche and Paulus 2000).

### 1.4 Aims of research

The primary aim of this thesis was to evaluate different pathways of enhancing core social cognitive processes such as understanding others (emotional facial recognition and mentalizing) and controlling oneself (emotion regulation). In study 1, we used a pharmacological approach and aimed at characterizing beneficial effects of intranasal OXT application on emotional facial recognition. In a double-blind, placebo-controlled design we explored the effect of a single intranasal administration of OXT on the ability to correctly identify basic emotional expressions. Given the role of OXT in modulating social motivational processes (Kemp and Guastella 2010; 2011), we were particularly interested in the effect of OXT on approach- and avoidance-related behavior. Hence, we clustered the basic emotional expressions of the emotion recognition task into approach-related emotions (happiness, surprise, anger) and avoidance-related emotions (fear, sadness, disgust). The facial stimuli were taken from the "Karolinska Directed Emotional Faces" set (KDEF set; Lundquist et al. 1998).

To further investigate the personal variability of OXT effects, we additionally tested in study 1 whether ELS experience would modulate the effects of OXT. Given the evidence

that the effects of OXT administration strongly depend on exposure to ELS, we aimed to evaluate whether participants with less ELS experience would show an improved recognition rate in the OXT condition as compared to participants with more ELS experience.

In study 2, we intended to investigate OXT induced effects on more complex emotions in a mentalizing task. In a double-blind, placebo-controlled design we explored the impact of a single intranasal administration of OXT on the performance in the „Reading the Mind in the Eye Test" (RMET, Baron-Cohen et al. 2001). Again, we aimed to further explore the variability of OXT effects. Based on studies that show more pronounced OXT effects in individuals with lower socio-cognitive skills (Bartz et al. 2011b), we included a measure for empathy. The rationale for this approach is derived from previous studies that have shown a strong relationship between mentalizing and empathy (Besel and Yuille 2010; Martin et al. 1996).

In study 3, we focused on a more elaborate process of social cognition, namely emotion regulation. Based on a large body of research suggesting that the dlPFC is engaged in cognitive reappraisal (Ochsner and Gross 2005), we applied tDCS, which has been shown to effectively modulate dlPFC activation (Keeser et al. 2011; Weber et al. 2014). We used this brain stimulation approach to investigate tDCS as a means to enhance cognitive reappraisal of negative pictures. In a double-blind, placebo-controlled design participants received either anodal tDCS over the dlPFC or sham tDCS during the performance of an emotion regulation task (Ochsner et al. 2004). Emotion regulation success was measured by skin conductance response (SCR) and behavioral arousal ratings. Given the importance of controlling for visual attentional deployment during a cognitive reappraisal task (van Reekum et al. 2007), we additionally measured gaze fixation.

# 2 The Beneficial Effect of Oxytocin on Avoidance-Related Facial Emotion Recognition Depends on Early Life Stress Experience

Feeser M, Fan Y, Weigand A, Hahn A, Gärtner M, Aust S, Böker H, Bajbouj M, Grimm S (2014) Psychopharmacology (Berl.) 231(24):4735-4744.

http://dx.doi.org/10.1007/s00213-014-3631-1

**Abstract**

Previous studies have shown that Oxytocin (OXT) enhances social cognitive processes. It has also been demonstrated that OXT does not uniformly facilitate social cognition. The effects of OXT administration strongly depend on the exposure to stressful experiences in early life. Emotional facial recognition is crucial for social cognition. However, no study has yet examined how the effects of OXT on the ability to identify emotional faces are altered by early life stress (ELS) experience. Given the role of OXT in modulating social motivational processes, we specifically aimed to investigate its effects on the recognition of approach- and avoidance-related facial emotions.

In a double-blind, between-subjects, placebo-controlled design, 82 male participants performed an emotion recognition task with faces taken from the "Karolinska Directed Emotional Faces" set. We clustered the six basic emotions along the dimensions approach (happy, surprise, anger) and avoidance (fear, sadness, disgust). ELS was assessed with the Childhood Trauma Questionnaire (CTQ).

Our results showed that OXT improved the ability to recognize avoidance-related emotional faces as compared to approach-related emotional faces. Whereas the performance for avoidance-related emotions in participants with higher ELS scores was comparable in both OXT and placebo condition, OXT enhanced emotion recognition in participants with lower ELS scores. Independent of OXT administration, we observed increased emotion recognition for avoidance-related faces in participants with high ELS scores.

Our findings suggest that the investigation of OXT on social recognition requires a broad approach that takes early life stress experiences as well as motivational processes into account.

## 2.1 Introduction

The neuropeptide oxytocin (OXT) plays a critical role in modulating attachment as well as social recognition in mammals (Bielsky and Young 2004; Donaldson and Young 2008; Ross and Young 2009). There is accumulating evidence that OXT also impacts human social behavior (Campbell 2010; Heinrichs et al. 2009). OXT is synthesized in the hypothalamus, which projects to limbic structures such as the amygdala, hippocampus, and midbrain, all structures that are involved in human social behavior and emotional processing (Meyer-Lindenberg et al. 2011). The use of intranasal OXT in experiments in humans has led to the promising hypothesis that OXT is capable of modulating a wide range of complex social cognitive functions. Specifically, previous studies have shown that OXT promotes social approach and trust (Baumgartner et al. 2008; Feldman et al. 2007; Kosfeld et al. 2005), reduces fear and anxiety (Heinrichs et al. 2003; Kirsch et al. 2005; Petrovic et al. 2008), enhances social memory (Guastella et al. 2008b; Savaskan et al. 2008; Weigand et al. 2013) and increases empathy (Hurlemann et al. 2010).

It has been suggested that the effects on prosocial behavior are associated with the role of OXT in decoding social signals such as facial expressions. Recent studies have demonstrated that OXT increases the ability to correctly identify emotional facial expressions (for a review see van Ijzendoorn et al. 2012). However, studies investigating the effect of OXT on distinct emotions have yielded mixed results. Although many studies demonstrate that OXT promotes the identification of happy faces (DiSimplicio et al. 2009; Marsh et al. 2010; Schulze et al. 2011), other studies also show beneficial effects on the recognition of fearful faces (Fischer-Shofty et al. 2010). Some studies indicated that OXT promotes the identification of emotions regardless of valence (Lischke et al. 2012; Prehn et al. 2013). Striepens et al. (2012) and Weigand et al. (2013) reported that OXT influenced the processing of negative emotional pictures. A recent meta-analysis by Shahrestani et al. (2013) has provided an overview about the impact of OXT application on the recognition of basic emotions. The authors conclude that the effects of OXT were more pronounced for happy and fearful facial expressions.

Besides its well-documented effects on enhancing the processing of emotional cues, other studies have suggested a more general role for OXT in modulating social motivation (Bartz and Hollander 2006). In this regard, Kemp and Guastella (2011) introduced the social-approach/withdrawal hypothesis. The authors suggested that OXT

may serve to increase approach-related behaviors (i.e. emotional engagement) while inhibiting withdrawal-related behaviors (i.e. anxiety, fear). According to this hypothesis, OXT effects are not explained by modulating the processing of distinct emotions, but are rather interpreted by acting on motivational behavior. This is in line with previous studies by Baumgartner et al. (2008) and Kosfeld et al. (2005) who proposed that OXT enhances trust by both decreasing the impact of betrayal adversity (withdrawal-related behavior) and increasing cooperation (approach-related behavior).

Growing evidence also highlights the important role of personal variability in social endocrinology (for reviews, see Bartz et al. 2011b; Olff et al. 2013). Specifically, previous studies demonstrated differential OXT-dependent effects as a function of personal or situational variables. For example, studies on social behavior indicated that the effects of OXT are to some extent context-dependent (De Dreu et al. 2010; Mikolajczak et al. 2010). Other studies showed that OXT effects were especially pronounced for subjects with low emotion regulation abilities (Quirin et al. 2011) as well as for subjects with high alexitymia scores (Luminet et al. 2011). The authors argue that a single dose of OXT does not have the same increment on socio-emotional abilities in everybody but rather depends on baseline socio-emotional abilities of the participants. Another recent study by Scheele et al. (2012) showed that the behavioral effects of OXT on social distance between males and females are moderated by personal characteristics such as relationship status. Following OXT application, only men in a monogamous relationship, but not single ones, avoided close personal proximity between themselves and another unfamiliar woman. The authors conclude that OXT may support to promote fidelity in human relationships.

In line with the above-mentioned findings on person-dependent oxytonergic effects, it has been suggested that the effects of OXT administration also depend on the personal family history of the participants, with stronger effects in individuals with a supportive family background (for a review, see Bakermans-Kranenburg and Van Ijzendoorn 2013). A recent study reported that the positive effects of OXT on prosocial behaviour in a social ostracism task toward a victim of social exclusion were limited to individuals with supportive family background (Riem et al. 2013). Furthermore, OXT increased the participants' willingness to donate money to a charity only in participants who experienced low levels of parental love withdrawal (Van Ijzendoorn et al. 2011). A moderating effect of adverse childhood experiences on the outcomes of OXT

administration was also reported by Meinlschmidt and Heim (2007). In a pilot study the authors showed that men with early parental separation exhibited attenuated decreases in cortisol after OXT application compared to the placebo group. To summarize, there is accumulating evidence that OXT effects on human social cognition and behavior are differential in individuals with experiences of maltreatment. This notion gains considerable support from studies investigating the impact of early life stress (ELS) on the oxytonergic system (Fries et al. 2005; Heim et al. 2009). These data indicate that early adverse social experiences might influence the development of the neuropeptide system and alter OXT receptor binding (Carter et al. 2008), thus resulting in differential responses to OXT. Even though emotional face recognition is a prerequisite of social cognition and behavior, no study has yet investigated whether ELS moderates OXT effects on the ability to identify emotional faces.

Regarding the association between emotion recognition abilities and ELS, there is empirical evidence for altered limbic brain activation in participants with a history of ELS. It has been reported that ELS is linked with enhanced amygdala responsiveness to sad faces in depressed patients (Grant et al. 2011) and to fearful faces in healthy subjects (Dannlowksi et al. 2012). With regard to facial emotion recognition, Pollak and Kistler (2009) found that physically abused children were able to accurately identify angry faces based on less perceptual information (such as activation of facial musculature) than controls. Other studies also reported that participants with a history of maltreatment showed superior recognition of faces displaying fear and sadness (Leist and Dadds 2009) and shorter reaction times when labeling fearful facial expressions (Masten et al. 2008).

In the present study, we aimed to investigate whether the effect of OXT administration on emotion recognition is modulated by ELS experience. Additionally, given the inconclusive results of previous research on oxytonergic effect on distinct emotions, we aimed to approach this research question from another angle. We therefore clustered the basic emotions used in our face recognition task along the dimensions approach and avoidance. These two dimensions represent core motivational systems that have been conceptualized as underlying emotion and behavior. The approach system drives the individual toward stimuli in the environment, whereas the avoidance system withholds the individual from these stimuli (Elliot and Covington 2001; Rutherford and Lindell

2011). The division of approach- (happiness, surprise, anger) and avoidance-related emotions (fear, sadness, disgust) is in line with previous studies that investigated the motivational value of basic emotions (Adam and Kleck 2005; Harmon-Jones et al. 2010). We predicted that the OXT effects would be more pronounced for avoidance-related emotions. This prediction is based on the following empirical findings: First, with regard to the role of OXT in promoting social approach (Bartz and Hollander 2006; Kemp and Guastella 2011), we expected that the effect might be more beneficial for emotional faces that require approach for successful identification, namely avoidance-related emotions. Second, given the results about enhanced recognition accuracy for fearful and sad faces in participants reporting maltreatment, we predicted to find similar results in our sample in participants reporting ELS.

Our study had two main objectives. First, we hypothesized that the effects of OXT would be more pronounced for avoidance-related emotions. Second, we aimed to further investigate whether the effects of OXT depend on a history of ELS. As mentioned above, previous studies suggested that OXT effects on social cognition are more pronounced in individuals without ELS experience. We therefore hypothesized that participants with lower ELS scores would show an improved recognition rate under OXT as compared to participants with higher ELS scores.

## 2.2 Methods

### 2.2.1 Subjects

82 male subjects, aged between 21 and 42 years (mean age= 27.9, SD= 4.7) participated in the study. Our study sample consisted of healthy participants that were recruited from the local university and community. All subjects were screened for psychiatric disorders using the short version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, SCID; Wittchen et al. 1997). Subjects with any history of psychiatric or neurological condition were excluded from the study.

We identified the participants' level of early life stress experiences via the Childhood Trauma Questionnaire (CTQ), which assesses experiences of childhood trauma continuously (rather than categorically). All participants were instructed to abstain from alcohol, caffeine and nicotine for 12 hours before testing as well as drinks and food (except water) for 2 hours before testing. Written 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.

### 2.2.2 Experimental design

The study was designed as a double-blind, between-subjects, placebo-controlled trial. Participants were randomly assigned to a group 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) participants self-administered three puffs per nostril with a dose of 24 international units (IU). All participants received either OXT (n= 41) or a placebo (n= 41) 45 minutes before the emotional facial recognition task. This dosage and waiting time correspond to previous studies investigating the effect of OXT on human behavioral effects (Domes et al. 2007b; Kirsch et al. 2005). To test the ability to recognize emotional faces, we applied a task containing emotional and neutral faces. We used a 2 (approach- vs. avoidance-related facial emotions) x 2 (OXT vs. placebo) experimental design and additionally tested whether early life stress assessed continuously would modulate the effects of OXT.

### 2.2.3 Emotion Recognition task

The facial stimuli were taken from the "Karolinska Directed Emotional Faces" set (KDEF set; Lundquist et al. 1998). This validated facial stimulus set (Goeleven et al. 2008) has previously been used in a number of social cognitive studies (Guastella et al. 2008b; Vuilleumier et al. 2003). Out of the KDEF set, a final sample of 56 face stimuli was selected for the present study. This sample corresponded to 8 models (4 females and 4 males). The facial stimuli contained emotional and neutral faces depicting one of six emotions, namely, fear, anger, disgust, sadness, happiness, surprise, and a neutral expression. To avoid priming effects, direct repetitions of a face from the same actor and repetitions of the same facial expression were excluded. As described earlier, the emotional expressions were later clustered into approach-related emotions (happiness, surprise, anger) and avoidance-related emotions (fear, sadness, disgust) for our analyses. 56 trials were presented during the experiment. Faces were presented one at a time with a grey background in the center of the computer screen and gazed directly at the participants. Each trial started with a fixation cross (1000 ms) followed by the

presentation of the face for 200 ms. After that, the seven facial expressions labels (6 emotion words plus neutral) were presented on the screen. Participants were instructed to identify the expression of each face and respond as quickly and accurately as possible by pressing one of seven labeled keys on a standard computer keyboard. Each labeled key corresponded to one facial expression. The maximum response time was set to 10 seconds. Three practice trials (seven facial expressions each) were completed at the beginning of the task to ensure appropriate understanding of the task. Each face was only shown once during the task. The maximum duration of the emotion recognition task was 10 minutes. The task was programmed and presented using the experimental control software Presentation (Neurobehavioral Systems Inc., Albany, CA).

### 2.2.4 Control variables

To ensure group matching with regard to interindividual differences participants completed the Mehrfach Wortschatz Intelligenztest, which measures verbal intelligence (MWT, Lehrl et al. 1995) and the NEO Five-Factor Inventory (NEO-FFI, Costa 1992). Additionally, a mood questionnaire was administered before OXT administration and after the task (Multidimensional Mood State Questionnaire, MDBF, Steyer et al. 1997). The MDBF provides a measure of the effect of OXT on mood, wakefulness, and calmness. In order to investigate whether ELS would moderate the effects of OXT, the Childhood Trauma Questionnaire (CTQ) was administered to assess early life stress (ELS). The CTQ (Bernstein and Fink 1998) is a 28-item retrospective self-report questionnaire designed to measure five types of adverse childhood experiences such as emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse. Scores range from 5 to 25 for each subscale with high scores indicating a strong exposure to early life stressors. There are no clearly defined cut-off scores to distinguish between participants with and without trauma. According to Scher et al. (2001), one possible distinction can be made between participants scoring high (above the 90$^{th}$ percentile = > 39 points on the CTQ) and low on CTQ (below the 50$^{th}$ percentile = < 29 points on the CTQ).

However, in order to increase statistical precision, we evaluated CTQ scores continuously in all analyses and avoided categorical groupings (Irwin and McClelland 2003). Hence, rather than creating groups, values were estimated within the GLM model for participants with high ELS (1SD above the mean of the Childhood Trauma

Questionnaire, CTQ) and low ELS (1SD below the mean of the Childhood Trauma Questionnaire). It is nonetheless important to note that the CTQ scores of our participants fell into Scher et al.'s (2001) categories of high and low CTQ scores (-1 SD = 28 points on the CTQ; +1 SD = 41 points on the CTQ).

### 2.2.5 Statistical analysis

For each trial the HIT rate (percent correct answers) was recorded. We then averaged the accuracy rates for avoidance-related emotional faces (fear, sadness, disgust) and for approach-related emotional faces (anger, surprise, happy). To test whether ELS moderates the effect of OXT on recognition accuracy, we first centered and standardized the total CTQ scores. We then performed a GLM analysis with group, the standardized continous CTQ score, and their interaction as the predictors. Accuracy rates for avoidance-related and approach-related faces were entered as two separate dependent variables. To test for experimental group differences for each emotional category, we additionally conducted t-test comparisons for each emotional facial expression.
Simple slopes for the relationship between ELS and accuracy scores per group (OXT vs. placebo) were analyzed by dummy-coding the group variable appropriately and repeating the analysis with these dummy-coded variables and their interactions with ELS in the model (Judd et al. 2009). The results are illustrated by estimating mean accuracy for participants with ELS scores 1 standard deviation (SD) above the mean as opposed to participants with ELS scores 1 SD below the mean. Statistical analyses were carried out using PASW (predictive Analytics SoftWare, Version 18.0, Chicago: SPSS Inc., Illinois, USA).

## 2.3 Results

### 2.3.1 Demographics and individual characteristics

The MWT showed that IQ levels of all subjects were in or above the range of the norm (M= 108.63, SD= 12.78). No significant differences between experimental groups with respect to age, verbal intelligence (MWT) and NEO-FFI scores were observed. Most importantly, there was no difference between the OXT and the placebo group regarding Childhood Trauma scores (CTQ). We also found no differences on the subscales of the

Multidimensional Mood State Questionnaire (MDBF) for the two experimental groups before and after the task. All group characteristics are reported in Table 1.

| | | Placebo group M (SD) | Oxytocin group M (SD) | t [a] | p value |
|---|---|---|---|---|---|
| **age** | | 28.6 (4.6) | 27.2 (4.7) | 1.306 | 0.195 |
| **MWT** | Total score | 108.5 (12.1) | 108.8 (13.6) | -0.103 | 0.918 |
| **NEO-FFI** | Neuroticism | 16.1 (6.2) | 18.4 (6.4) | 0.823 | 0.423 |
| | Extraversion | 27.37 (7.4) | 29.1 (7.0) | -1.096 | 0.276 |
| | Openness | 32.6 (8.2) | 32.9 (8.0) | -0.136 | 0.892 |
| | Agreeableness | 31.5 (5.5) | 30.3 (5.5) | 0.947 | 0.347 |
| | Conscientiousness | 30.7 (8.5) | 31.6 (7.2) | -0.548 | 0.585 |
| **CTQ** | Total score | 36.7 (8.3) | 37.6 (9.3) | -0.902 | 0.370 |
| | Emotional Neglect | 9.1 (3.7) | 9.8 (4.0) | -0.798 | 0.427 |
| | Emotional Abuse | 7.0 (3.0) | 7.6 (3.1) | -0.833 | 0.407 |
| | Physical Neglect | 6.7 (2.5) | 7.5 (3.3) | -1.298 | 0.198 |
| | Physical Abuse | 5.7 (1.4) | 5.8 (2.3) | -0.291 | 0.772 |
| | Sexual Abuse | 5.4 (2.2) | 5.1 (0.6) | 0.817 | 0.416 |
| **MDBF pre** | Elevated vs. Depressed mood | 15.5 (3.1) | 16.4 (2.5) | -1.114 | 0.272 |
| | Wakefulness vs. Sleepiness | 13.7 (4.3) | 14.6 (3.4) | -0.807 | 0.424 |
| | Calmness vs. Restlessness | 15.3 (3.0) | 16.6 (3.0) | -1.513 | 0.138 |
| **MDBF post** | Elevated vs. Depressed mood | 14.8 (3.5) | 15.1 (3.7) | -0.351 | 0.727 |
| | Wakefulness vs. Sleepiness | 12.4 (2.9) | 12.9 (3.9) | -0.424 | 0.674 |
| | Calmness vs. Restlessness | 15.1 (2.8) | 15.0 (3.3) | 0.052 | 0.959 |

**Tab. 1**

Demographics and individual characteristics. M mean, SD standard deviation, MWT Mehrfach Wortschatz Intelligenztest (verbal intelligence test) , NEO-FFI Neo Five-Factor Inventory, CTQ Childhood Trauma Questionnaire, MDBF Multidimensional Mood State Questionnaire. [a] Independent samples t tests, two-tailed

We also tested whether ELS was correlated with any of the variables presented in Table 1. We only found a theoretically consistent significant positive correlation between ELS and Neuroticism ($r(80) = .29$, $p < .001$), indicating that participants who reported having experienced more childhood trauma were more neurotic. However, despite this relationship controlling for Neuroticism in our main analyses did not alter any of the results. No other relationships between the variables assessed and ELS were significant (all p values > 0.05).

### 2.3.2 Accuracy

A main effect of group (OXT vs placebo) was observed for accuracy in avoidance-related emotional faces [$F(1, 78)= 7.72$, $p= .007$]. We found higher accuracy rates for subjects in the OXT group ($M= 0.64$ , $SD= .11$) as compared to the placebo group ($M=0.57$, $SD= .12$) (see Figure 4).

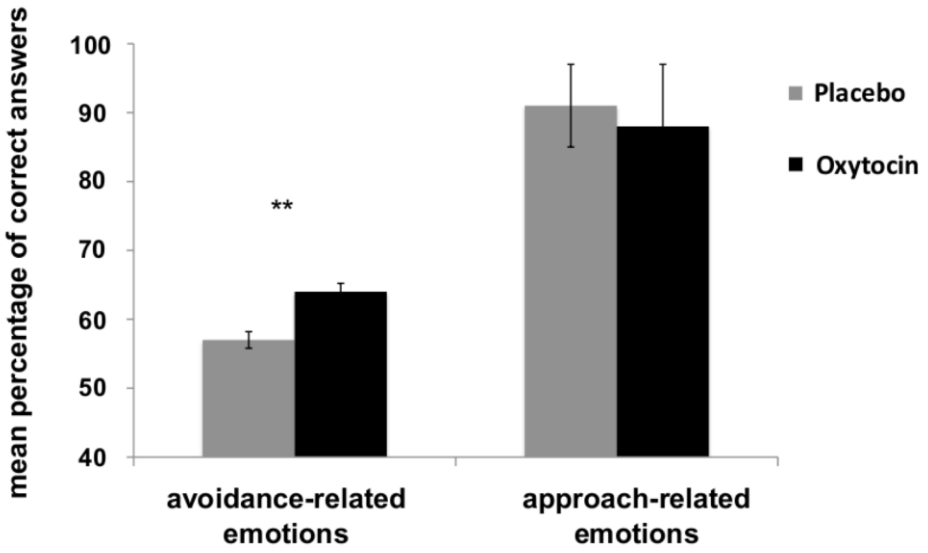


**Fig. 4**

Mean percentage of correct answers for both groups (OXT vs. placebo) and motivational value (avoidance-related emotions, approach-related emotions). * indicate significant post-hoc comparisons (** $p < 0.01$). Bars represent mean percentage ± standard error of mean.

T-test comparisons (OXT vs placebo) for each emotional category revealed higher accuracy rates for fearful faces in the OXT group ($M= 0.46$, $SD= .23$) as compared to the placebo group ($M= 0.35$, $SD= .22$; $t(80)= -2.07$, $p = .042$). We also observed a trend for higher accuracy rates for disgust faces in the OXT group ($M= 0.67$, $SD= .20$) as compared

to the placebo group (M= 0.60, SD= .16; t(80)= -1.80, p = .077). Further t-tests revealed no differences between the two experimental groups in accuracy rates for angry faces (OXT: M= 0.78, SD= .18; placebo: M= 0.83, SD= .14; t(80)= 1.23, p > 0.05), for happy faces (OXT: M= 0.96, SD= .07; placebo: M= 0.96, SD= .06; t(80)= 0.63, p > 0.05), for sad faces (OXT: M= 0.80, SD= .16; placebo: M= 0.76, SD= .19; t(80)= -0.96, p > 0.05) or for surprised faces (OXT: M= 0.91, SD= .12; placebo: M= 0.93, SD= .11; t(80)= 0.62, p > 0.05).

Importantly, confirming our hypotheses on the moderating effects of ELS on accuracy, the analysis revealed an interaction of group and Early Life Stress assessed continuously on accuracy for avoidance-related emotions [F(1, 78)= 4.86, p= 0.031]. Specifically, for subjects with an ELS score 1 SD below the mean, follow-up analyses revealed higher accuracy in the OXT group (M= 0.67, SD= 0.025) as compared to the placebo group (M= 0.53, SD= 0.024, F(1, 78)= 12.58, p= 0.001). In contrast, no group differences were found for subjects with an ELS score 1 SD above the mean (p > .05). In other words, whereas participants with higher ELS scores identified facial emotions equally accurately in both OXT and placebo groups, participants scoring low on ELS performed better under OXT as compared to placebo.

Looking at the same interaction in a different way, simple slopes analyses revealed no significant relationship between ELS and accuracy for the OXT group, b=-.016, t(78) =-.99, p=.32, but a significant positive relationship for the placebo group b=.039, t(78)=2.05, p=.044. That is, as displayed in Figure 5, the group-by-ELS interaction was driven by an increase in accuracy among placebo participants who reported higher ELS levels, whereas ELS had no effect on participants in the OXT group. This also indicates that whereas participants with higher ELS scores identified facial emotions equally accurately in both OXT and placebo groups, participants scoring low on ELS performed better under OXT as compared to placebo.

In the next step we analyzed the accuracy for approach-related emotional faces. There was no main effect for accuracy in approach-related emotional faces [F(1, 78)= 1.68, p= 0.19]. Furthermore, no interaction of group and Early Life Stress on accuracy for approach-related emotions was found [F(1, 78)= 0.80, p= 0.37].

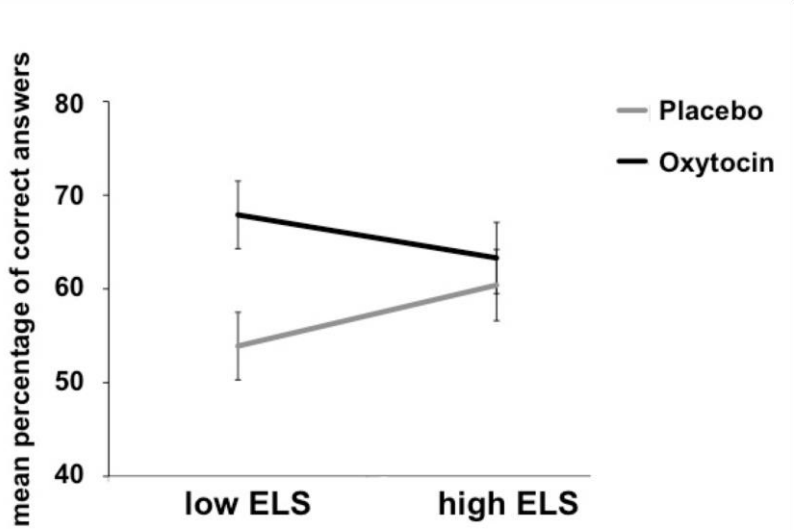


**Fig. 5**

Mean percentage of correct answers as a function of early life stress (ELS) scores measured by the Childhood Trauma Questionnaire (CTQ, Bernstein & Fink, 1998) and the experimental group (OXT vs. placebo).
low ELS= mean percentage of correct answers for participants scoring 1 standard deviation below the mean on the Childhood Trauma Questionnaire; high ELS= mean percentage of correct answers for participants scoring 1 standard deviation above the mean on the Childhood Trauma Questionnaire.

## 2.4 Discussion

The aim of the present study was to investigate the effect of OXT on approach- and avoidance-related emotion recognition in participants reporting high and low levels of ELS. The study yielded three main results. First, as hypothesized, a single dose of intranasally administered OXT improved the ability to recognize avoidance-related emotional expressions. Second, this effect was more pronounced for participants with low ELS scores. Third, in the placebo group recognition accuracy was higher in participants who reported more severe ELS. It is important to note that the observed results cannot be explained by general effects of OXT on mood, wakefulness and calmness since there were no differences between the two experimental groups in the MDBF before and after the task. More importantly, the OXT versus the placebo group did not differ in their CTQ scores. This rules out the possibility that the effects are biased by group differences in ELS experiences.

There are several possible explanations for the observed effects of OXT on emotion recognition for avoidance-related emotions. Our finding is compatible with previous studies reporting that OXT drives the desire for social approach, social affiliation and attachment (for a review see Heinrichs et al. 2009). As expected, the effect of OXT seems to be more beneficial for emotional faces that require approach for successful identification, namely avoidance-related emotions. Apparently, the effect of OXT on emotion recognition depends on motivational processes to approach or avoid the presented stimuli. To support this notion, a recent study by Striepens et al. (2012) showed that OXT administration potentiated acoustic startle responses and subsequent memory to negative stimuli. The authors discuss these findings by suggesting that OXT promotes approach behavior towards other individuals displaying negative emotional signals. In line with this, Weigand et al. (2013) showed that OXT enhances the processing of negative social stimuli during memory encoding and retrieval.

One might also hypothesize that OXT enhances emotional facial recognition by increasing the perceptual salience processing of social cues. Supporting this hypothesis, a recent study showed that OXT promotes the detection of very briefly presented emotional faces (Schulze et al. 2011). OXT also increases gaze to the eye region, thus accentuating cues that are highly relevant for interpersonal communication (Andari et al. 2010; Guastella et al. 2008a). Furthermore, better emotion recognition after OXT administration is associated with increased pupil dilation, suggesting that OXT promotes the allocation of attentional resources during processing of emotional salient facial expressions (Prehn et al. 2013). The assumption that OXT enhances the salience of social cues also gains considerable support from animal studies. Previous results indicate that OXT modulates the salience of social cues by boosting the dopamine system (Melis et al. 2007; Shahrokh et al. 2010). In humans, Groppe et al. (2013) recently found that OXT enhances activation in the ventral tegmental area (VTA), a brain region rich in OXT receptors (Loup et al. 1991) in response to social cues. The VTA plays a crucial rule in processing the salience of social cues as dopamine neurons project from the VTA to the nucleus accumbens (Bromberg et al. 2010).

Regarding the result that especially participants with low ELS benefited most from OXT administration, our data is in line with previous studies indicating that oxytonergic effects on prosocial behaviour are lowered or absent in individuals with adverse experiences during childhood. This points to environmentally induced changes of the

oxytonergic system (Bartz et al. 2011b). As described earlier, the effects of OXT seem to be strongly dependent on individual experiences and personality traits. A potential neurobiological mechanism for this interpretation is described in a recent review by Bakermans-Kranenburg and van Ijzendoorn (2013). It seems possible that early adverse childhood experiences alter the methylation level of the OXT receptor, thus affecting the system's functioning. Methylation of the receptor gene decreases OXT levels and may block the common mechanisms after intranasally administered OXT. This may in turn lead to decreased sensitivity for OXT administration.

To keep with this idea, Fries et al. (2005) reported decreased urinary concentrations of OXT in maltreated children. Decreased cerebrospinal fluid (CSF) OXT concentrations have also been measured in adult women with ELS experience (Heim et al. 2009). These findings are consistent with animal studies investigating the effect of maladaptive early nurturing experiences on the alterations in OXT receptor levels in rats (Francis et al. 2000) and decreased CSF OXT concentrations in nursery-reared monkeys as compared with mother-reared controls (Winslow et al. 2003).

As we did not investigate the neurobiological mechanisms underlying the effect of OXT on emotion recognition, we can only suggest theoretical models. However, a number of studies have already identified brain regions associated with OXT effects on human social cognition (Domes et al. 2007a; Kirsch et al. 2005). They support the view that OXT effects are modulated by limbic brain regions with the amygdala as a core structure (Meyer-Lindenberg et al. 2011). The amygdala links the perception of stimuli to an emotional response and modulates cognitive processes on the basis of the value of the perceived stimulus (Adolphs 2009; Anderson and Phelphs 2001).

A number of studies have consistently reported that early life stress (ELS) is associated with hyperactivation in limbic brain regions during emotion processing. Specifically, it has been shown that ELS is linked with enhanced amygdala responsiveness to sad faces in depressed patients (Grant et al. 2011), to fearful faces in healthy subjects (Dannlowksi et al. 2012) and to threatening faces in emotionally neglected youths (Maheu et al. 2010; Tottenham et al. 2011). These lines of evidence suggest a crucial effect of ELS on amygdala excitability to negative facial expressions that seems to persist through the lifespan.

Given the above-mentioned role of OXT in enhancing subjects' attention to social cues, one might speculate that OXT administration might be derogatory to individuals who

are already hypersensitive to social cues such as subjects reporting ELS. It has been found that OXT prohibited trust and prosocial behavior depending on chronic interpersonal insecurities (Bartz et al. 2011a). To summarize, whether OXT promotes or hinders prosocial behaviour and social cognition seems to depend on the individuals and their social experiences. In other words, OXT may facilitate prosocial behavior and social cognition but an adverse personal history may reduce these potentially beneficial effects.

In the placebo but not in the OXT group, we also observed increased performance in participants reporting high levels of ELS. This finding supports previous work indicating that participants with a history of maltreatment show an increased sensitivity for negative faces (Dannlowski et al. 2012; Grant et al. 2011). Furthermore, a superior recognition of faces displaying fear and sadness (Leist and Dadds 2009) and shorter reaction times when labeling fearful facial expressions (Masten et al. 2008) was demonstrated. Prior learning plays an important role in how facial expression displays are classified into distinct emotion categories (Pollak and Kistler 2002). The strength of accurately recognizing facial expressions largely depends on the frequency and intensity of exposure to different expressions (Pollak et al. 2009). Thus, enhanced recognition of avoidance-related emotions may stem from a more extensive personal experience of these emotions in participants reporting ELS. For example, increased ability to recognize avoidance-related emotions such as fear and sadness on a parent or sibling´s face might support the ability to identify threatening situations in the environment.

There are some limitations that need to be acknowledged. First, our facial stimuli were not animated. To increase ecological validity, future studies should develop experimental tasks including more interpersonal situation and real-life contexts. Another limitation lies in the fact that we only included male participants. Previous studies have reported gender differences in OXT dependent effects (Domes et al. 2010; Lischke et al. 2012b) indicating that our results might not be generalizable to women. Future studies should address this issue by investigating both male and female participants. Regarding the assessment of ELS in this sample, it is important to acknowledge the subjectivity of self-reported ELS. Our design would have benefited from more detailed measurement of ELS, for example using early childhood stress interviews.

The ability to accurately recognize facial expressions of emotions plays a crucial role for interpersonal communication and has significant implications for adaptive social functioning. We demonstrate that OXT enhances the recognition of avoidance-related emotional facial expressions. However, our data also suggests that OXT does not uniformly facilitate emotion recognition in humans. These results highlight the importance of considering both differences in participants´ early life experiences and motivational processes when evaluating the potential of OXT in targeting social cognition.

# 3 Oxytocin Improves Mentalizing – Pronounced Effects for Individuals with Attenuated Ability to Empathize

Feeser M, Fan Y, Weigand A, Hahn A, Gärtner M, Böker H, Grimm S, Bajbouj M (2015) Psychoneuroendocrinology (in minor revision).

**Abstract**

The ability to predict the behavior of others based on their mental states is crucial for social functioning. Previous studies have provided evidence for the role of Oxytocin (OXT) in enhancing the ability to mentalize. It has also been demonstrated that the effect of OXT seems to strongly depend on socio-cognitive skills with more pronounced effects in individuals with lower socio-cognitive skills. Although recent studies indicate that mentalizing is related to empathy, no study has yet examined whether the effects of OXT on mentalizing depend on the ability to empathize.

71 male participants participated in a double-blind, between-subjects, placebo-controlled experiment. The Reading the Mind in the Eye Test (RMET) was used to investigate mentalizing abilities. We analyzed the effect of OXT on easy and difficult items of the RMET depending on differential empathy scores of the participants as assessed with the Empathy Quotient (EQ).

Our results showed that OXT improves mentalizing for difficult but not for easy items. Whereas the performance in participants with higher empathy scores was comparable in both OXT and placebo condition, OXT specifically enhanced mentalizing accuracy for difficult items in participants with lower empathy scores. Independent of OXT administration, we observed increased mentalizing accuracy for difficult items in participants with higher empathy scores .

Our findings suggest that OXT enhances mentalizing abilities. However, we also demonstrate that not all participants benefited from OXT application. It seems that the effects of OXT strongly depend on baseline social-cognitive skills such as empathy.

## 3.1 Introduction

The ability to identify internal states of another person plays an important role in human social cognition (Humphrey 1976). During social interactions, humans need to perceive, represent and reason about their own and others' intentions. This ability is called 'mentalizing' (Frith and Frith 2006). Mentalizing implies the ability to infer mental and emotional states from multiple sources, e.g. understanding the other person´s perspectives and beliefs, as well as interpreting non-verbal cues such as facial expressions and gaze direction (Baron-Cohen 1995). The foundation for mentalizing is partly rooted in infant-caregiving attachment relationships and matures over the lifespan with increased interpersonal interactions (Fonagy et al. 2007).

Several studies have shown the strong relationship between mentalizing and empathy (Besel and Yuille 2010; Martin et al. 1996). Findings from neuroimaging studies suggest that greater neural activity in brain circuits underlying mentalizing is related to more self-reported empathy (Hooker et al. 2008; Hooker et al. 2013). Even though mentalizing and empathy are often used as synonyms, they represent different skills that rely on distinct neuronal circuitries (Singer 2006). Empathy describes the capacity to sense the feelings of others and relies on somatosensory and insular cortices as well as limbic areas and anterior cingulate cortex (Singer 2006). In contrast, mentalizing refers to the ability to understand other people´s behavior, such as their intentions, goals, and beliefs. It relies on structures of the prefrontal cortex, superior temporal sulcus (STS), the temporo-parietal junction (TPJ) and the anterior temporal poles (TP) (Saxe et al. 2004; Frith and Frith 2006b). Furthermore, mentalizing and empathy display distinct ontogenetic trajectories (Baron-Cohen et al. 2000). In particular, it has been suggested that empathy develops much earlier than mentalizing, because it depends on limbic structures that mature early in ontogony (Singer 2006).

Previous work has furthered insight into the processes underlying mentalizing (Frith and Frith 2006). Especially non-verbal information from the eyes conveys a rich source of social information that is important in mentalizing processes (Blair 2003). Baron-Cohen et al. (2000) show that humans are able to quickly and accurately decode another person´s complex mental state based on facial cues.

Individual differences in the ability to mentalize can be investigated with the Reading the Mind in the Eye Test (RMET, Baron-Cohen et al. 2001). The RMET requires participants to infer internal states of another individual from subtle differences in the

eye region. The test´s validity has been proven in healthy subjects (Hysek et al. 2012; Luminet et al. 2011; Moor et al. 2012) and clinical studies with autistic patients (Baron-Cohen et al. 2001; Craig et al. 2004; Guastella et al. 2010).

A means to enhance social cognition including mentalizing, is the neuropeptide Oxytocin (OXT, Campbell, 2010; Heinrichs et al. 2009). Previous work suggests that OXT plays an important role in the modulation of human behavior (Meyer-Lindenberg et al. 2011). OXT receptors are found in brain structures that are involved in human social behavior and emotional processing, including the amygdala, striatum, hippocampus, nucleus accumbens and midbrain (Meyer-Lindenberg et al. 2011). The use of intranasal OXT in experiments in humans has led to the promising hypothesis that OXT is capable of modulating a wide range of complex social-cognitive functions. Specifically, previous studies have shown that OXT facilitates social memory (Guastella et al. 2008b; Savaskan et al. 2008; Weigand et al. 2013), reduces fear and anxiety (Heinrichs et al. 2003; Kirsch et al. 2005), and promotes social approach and trust (Baumgartner et al. 2008; Feldmann et al. 2007; Kosfeld et al. 2005). OXT administration has also been shown to enhance empathy (Hurlemann et al. 2010).

Regarding the role of facial expressions detection in mentalizing, a number of studies have also provided evidence for the role of OXT in enhancing facial emotion recognition (for a review see van Ijzendoorn and Bakermans-Kranenburg 2012). They demonstrate that OXT promotes the identification of happy faces (DiSimplicio et al. 2009; Guastella et al. 2008b; Marsh et al. 2010, Schulze et al. 2011), whereas other studies also show beneficial effects on the recognition of fearful faces (Fischer-Shofty et al. 2010). Some studies indicate that OXT promotes the identification of emotions regardless of valence (Lischke et al. 2012a; Prehn et al. 2013).

Most important for the present study, it has repeatedly been shown that OXT specifically increases mentalizing in healthy participants (Domes et al. 2007b, Luminet et al. 2011) and participants with autism spectrum disorder (Anagnostou et al. 2012). Domes et al. (2007b) investigated the effect of OXT on the ability to mentalize using the RMET. The authors demonstrated that OXT compared with placebo increases the percentage of correct answers. Notably, this effect was only observed for difficult items in contrast to easy items. That is, the RMET was formerly designed to investigate severe impairments in mentalizing abilities in adults with autism spectrum disorders. In order to prevent possible ceiling effects in studies with healthy adults, the authors hence split the 36

items into two subsets of easy and difficult items. Luminet et al. (2010) also showed beneficial effects of OXT on the accuracy of the RMET. Interestingly, the authors reported that the effects were especially pronounced for subjects with high alexithymia scores.

This finding is in line with previous studies that highlight the important role of personal variability in social endocrinology (for reviews, see Bartz et al. 2011b; Olff et al. 2013). For example, Quirin et al. (2011) demonstrated that the effect of OXT on stress-contingent cortisol release depends on baseline emotion regulation abilities. Specifically, subjects with low emotion regulation abilities benefit from OXT application. In line with this, Bartz et al. (2010) reported that OXT effects on empathic accuracy are proportional to the level of autistic traits of the participants. The authors conclude that OXT only improves empathic accuracy for participants who are less socially proficient at baseline. To support this notion, a recent study by Leknes and colleagues (2013) showed that differences in baseline emotional sensitivity predict the effects of OXT on the accuracy rate for hidden emotional expressions (Leknes et al. 2013). Participants with low performance-based emotional sensitivity showed greater task improvement following OXT application. Grimm et al. (2014) demonstrated that the effects of OXT during psychosocial stress strongly depend on early life experiences of the participants.

To summarize, there is accumulating evidence that the degree to which individuals are susceptible to OXT application is not uniform but varies substantially. Considering the above-mentioned social-cognitive competencies that are moderating the effect of OXT, it is remarkable that no study has yet directly tested whether the ability to empathize influences the effect of OXT application. For example, several studies have shown the strong relationship between empathy and facial recognition underlying mentalizing. Specifically, participants with higher empathy scores were able to identify facial expressions more accurately (Besel and Yuille, 2010; Martin et al. 1996). Given the relationship between empathy and mentalizing as well as the personal variability in OXT-induced effects, the present study aimed at investigating whether the effect of OXT depends on individual empathy scores of the participants. Previous studies demonstrated the effect of OXT in particular for participants with low socio-emotional skills (Bartz et al. 2010; Leknes et al. 2013; Luminet et al. 2010; Quirin et al. 2011). We therefore expected similar findings in our sample in participants with lower empathy scores.

Our study had two main objectives. First, we aimed to replicate previous findings on the role of OXT in enhancing mentalizing. Given the results by Domes et al. (2007b), we predicted that OXT-induced effects would be more pronounced for difficult items as compared to easy items. Second, we aimed to further investigate whether the effect of OXT on mentalizing is moderated by individual differences in the ability to empathize as measured with the Empathy Quotient (EQ; Baron-Cohen and Wheelwright, 2004). We hypothesized that participants with lower empathy scores would benefit more from OXT application as opposed to participants with higher empathy scores.

## 3.2 Methods

### 3.2.1 Subjects

71 male subjects, aged between 21 and 42 years (mean age= 28.1, SD= 4.8) participated in the study. Our study sample consisted of healthy participants that were recruited from the local university and community. All subjects were screened for psychiatric disorders using the short version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, SCID, Wittchen et al. 1997). Subjects with any history of psychiatric or neurological condition were excluded from the study.
We identified the participants' ability to empathize via the Empathy Quotient (EQ, Baron-Cohen and Wheelwright 2004), which assesses empathy continuously (rather than categorically). All participants were instructed to abstain from alcohol, caffeine and nicotine for 12 hours before testing, as well as from drinks and food (except water) for 2 hours before testing. Written 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.

### 3.2.2 Experimental design

The study was designed as a double-blind, between-subjects, placebo-controlled trial. Participants were randomly assigned to a group 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) participants self-administered three puffs per nostril with a dose of 24 international units (IU). All

participants received either OXT (n= 36) or a placebo (n= 35) 45 minutes before the task. This dosage and waiting time correspond to previous studies investigating the effect of OXT on human behavioral effects (Domes et al. 2007b; Kirsch et al. 2005). To test the ability to infer mental states in others, we applied the RMET (Baron-Cohen et al. 2001). We used a 2 (easy vs. difficult items) x 2 (OXT vs. placebo) experimental design with repeated measures on the first factor, and additionally tested whether empathy assessed continuously would moderate the effects of OXT.

### 3.2.3 Reading the Mind in the Eye task (RMET)

The RMET consisted of 36 photographs of the eye region expressing a complex mental state. Photographs were presented one at a time with a grey background in the center of the computer screen. Each trial started with a fixation cross (1000 ms), followed by the presentation of the face. Each face remained on the screen until the participant made a response. The maximum response time was set to 20 seconds. Four mental states labels (one target label and three distractor labels) were simultaneously presented on the screen. Participants were instructed to identify the mental state and respond as quickly and accurately as possible by pressing one of four keys on a standard computer keyboard. Each labeled key corresponded to one mental state. Four practice trials were completed at the beginning of the task to ensure appropriate understanding of the task. Each photograph was only shown once during the task. The maximum duration of the task was 13 minutes. An example trial of the RMET is displayed in Figure 6. The task was programmed and presented using the experimental control software Presentation (Neurobehavioral Systems Inc., Albany, CA).

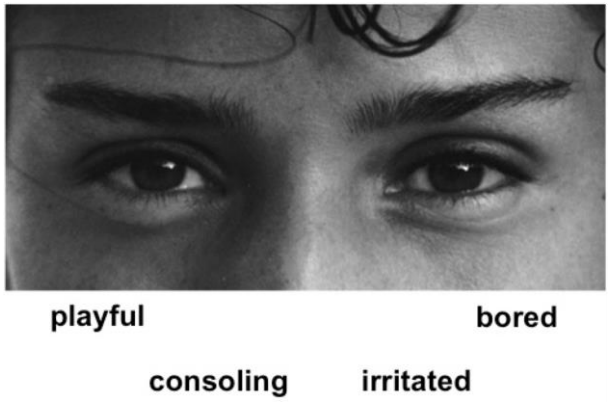


**Fig. 6**

Example trial of the Reading the mind in the Eye Test (RMET, Baron-Cohen et al. 2001)

### 3.2.4 Control variables

To ensure group matching with regard to inter-individual differences, participants completed the Mehrfach Wortschatz Intelligenztest, which measures verbal intelligence (MWT, Lehrl et al. 1995) and the NEO Five-Factor Inventory (NEO-FFI, Costa 1992). Additionally, a mood questionnaire was administered before OXT administration and after the task (Multidimensional Mood State Questionnaire, MDBF, Steyer et al. 1997). The MDBF provides a measure of the effect of OXT on mood, wakefulness and calmness. In order to investigate whether empathy would moderate the effects of OXT, we used the Empathy Quotient (EQ, Baron-Cohen and Wheelwright 2004) to assess the ability to empathize. The EQ is a 60-item self-report questionnaire which consists of 40 empathy items and 20 control items. The total score can be split into the subscales Cognitive Empathy, Social Skills and Emotional Reactivity.

To increase statistical precision, we evaluated total EQ scores continuously in all analyses and avoided categorical groupings (Irwin and McClelland 2003). Hence, rather than creating groups, values were estimated within the GLM model for participants with high total EQ (1SD above the mean of the Empathy Quotient) and low total EQ (1SD below the mean of the Empathy Quotient).

### 3.2.5 Statistical analysis

For each trial the HIT rate (percent correct answers) was recorded. To test whether empathy moderates the effect of OXT on mentalizing accuracy, we first centered and standardized the EQ scores. In order to investigate OXT effects as a function of task difficulty, we split the 36 items of the RMET into two subsets of easy and difficult items (Domes et al. 2007b). We then performed a GLM analysis using group (OXT vs. placebo), the standardized EQ scores and their interaction as the predictors. In order to investigate the relationship between empathy and accuracy scores separately per group (OXT vs. placebo), simple slopes were analyzed by dummy-coding the group variable appropriately and repeating the analysis with these dummy-coded variables, EQ, and their interactions, in the model (Judd et al. 2009). The results are illustrated by estimating mean accuracy for participants with EQ scores 1 standard deviation (SD) above the mean and participants with EQ scores 1 SD below the mean. Statistical analyses were carried out using PASW (predictive Analytics SoftWare, Version 18.0, Chicago: SPSS Inc., Illinois, USA).

## 3.3 Results

### 3.3.1 Demographics and individual characteristics

After screening for outliers, data from four subjects were excluded from the analyses, because their overall task accuracy was more than 2.5 SD below the mean. The final sample size was 67 (n= 33 OXT and n= 34 placebo). The MWT scores showed that IQ levels of all subjects were in or above the range of the norm (M= 108.49, SD= 11.96). No significant differences between experimental groups with respect to age, verbal intelligence (MWT) and NEO-FFI scores were observed. Most importantly, there was no difference between the OXT and the placebo group regarding the EQ scores. We also found no differences on the subscales of the Multidimensional Mood State Questionnaire (MDBF) for the two experimental groups before and after the task. All group characteristics are reported in Table 2.

| | | Placebo group M (SD) | Oxytocin group M (SD) | t [a] | p value |
|---|---|---|---|---|---|
| **age** | | 28.9 (4.8) | 27.2 (4.9) | 1.542 | 0.128 |
| **MWT** | Total score | 107.1 (11.2) | 109.9 (12.7) | -0.975 | 0.333 |
| **NEO-FFI** | Neuroticism | 21.6 (9.2) | 17.7 (9.4) | 1.714 | 0.091 |
| | Extraversion | 27.9 (7.2) | 29.6 (7.2) | -0.961 | 0.340 |
| | Openness | 32.1 (8.3) | 32.9 (7.7) | -0.464 | 0.645 |
| | Agreeableness | 32.0 (5.0) | 30.6 (5.6) | 1.099 | 0.276 |
| | Conscientiousness | 32.0 (5.0) | 30.6 (5.6) | -0.328 | 0.744 |
| **EQ** | Total score | 37.7 (8.4) | 38.4 (9.0) | -0.324 | 0.747 |
| | Cognitive Empathy | 4.7 (1.9) | 4.7 (2.0) | 0.080 | 0.937 |
| | Social Skills | 6.2 (1.7) | 6.2 (1.5) | -0.092 | 0.927 |
| | Emotional Reactivity | 5.6 (1.8) | 5.0 (2.1) | 1.212 | 0.230 |
| **MDBF pre** | Elevated vs. Depressed mood | 15.4 (3.1) | 16.3 (2.4) | -0.886 | 0.382 |
| | Wakefulness vs. Sleepiness | 13.6 (4.2) | 14.6 (3.4) | -0.757 | 0.454 |
| | Calmness vs. Restlessness | 15.3 (3.2) | 16.5 (3.0) | -1.269 | 0.212 |

| | | | | | |
|---|---|---|---|---|---|
| **MDBF post** | Elevated vs. Depressed mood | 15.2 (3.2) | 15.0 (3.7) | 0.196 | 0.846 |
| | Wakefulness vs. Sleepiness | 12.5 (3.0) | 12.8 (4.0) | -0.259 | 0.797 |
| | Calmness vs. Restlessness | 15.6 (2.5) | 14.9 (3.4) | 0.679 | 0.502 |

**Tab. 2**

Demographics and individual characteristics. M mean, SD standard deviation, MWT Mehrfach Wortschatz Intelligenztest (verbal intelligence test) , NEO-FFI Neo Five-Factor Inventory, EQ Empathy Quotient, MDBF Multidimensional Mood State Questionnaire.
[a] Independent samples t tests, two-tailed

### 3.3.2 Accuracy

A main effect of group (OXT vs. placebo) was observed for mentalizing accuracy for difficult items [F(1, 63)= 12.60, p= .001]. We observed higher accuracy rates in the OXT group (M= 0.72, SD= 0.11) as compared to the placebo group (M=0.64, SD= 0.12; t(65)= -3.29, p= 0.002). No main effect of group (OXT vs. placebo) was found for mentalizing accuracy for easy items [F(1, 63)= 0.03, p > 0.05] (see Figure 7).

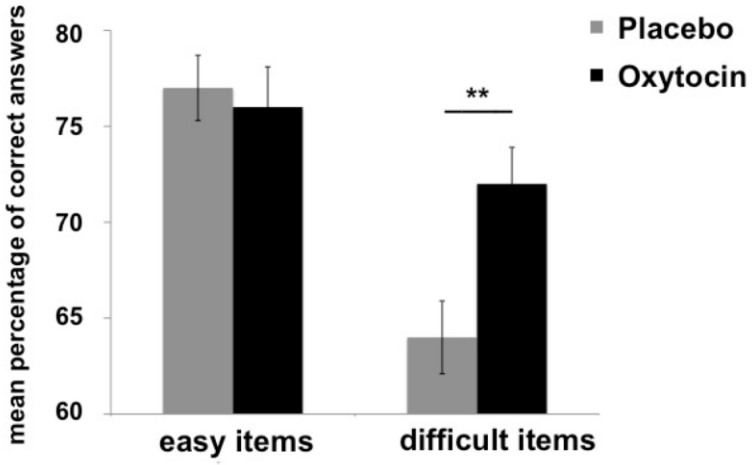


**Fig. 7**

Mean percentage of correct answers for both groups (OXT vs. placebo) and item difficulty (easy items, difficult items). * indicate significant post-hoc comparisons (** p < 0.01). Bars represent mean percentage ± standard error of mean.

Confirming our hypothesis on the moderating effects of empathy on mentalizing accuracy, the analysis revealed an interaction of group (OXT vs. placebo) and empathy

assessed continuously on mentalizing accuracy for difficult items [F(1, 63)= 4.50, p= 0.038] (see Figure 8).

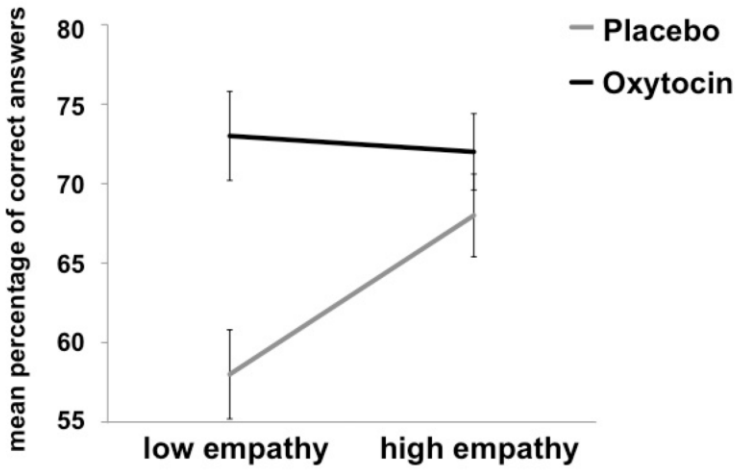


**Fig. 8**

Mean percentage of correct answers for difficult items as a function of empathy scores measured by the Empathy Quotient (EQ, Baron-Cohen & Wheelwright, 2004) and the experimental group (OXT vs. placebo). Bars represent mean percentage ± standard error of mean. Low empathy = mean percentage of correct answers for participants scoring 1 standard deviation below the mean on the Empathy Quotient; high empathy = mean percentage of correct answers for participants scoring 1 standard deviation above the mean on the Empathy Quotient.

Specifically, for participants with an EQ score 1 SD below the mean, follow-up analyses revealed higher accuracy in the OXT group for difficult items (M= 0.73, SD= 0.09) as compared to the placebo group (M= 0.58 SD= 0.08; F(1, 63)= 14.48, p < 0.001). In contrast, no group differences were found for subjects with an EQ score 1 SD above the mean for difficult items (OXT group: (M= 0.72, SD= 0.12); placebo group: (M= 0.68, SD= 0.11; F(1, 63)= 1.07, p > 0.05). This indicates that whereas participants with higher empathy scores identified facial emotions equally accurate in both OXT and placebo groups, participants with lower empathy scores performed better under OXT as compared to placebo.

Another way to investigate the same group-by-EQ interaction is to look at the relationship between empathy and accuracy scores separately per group (OXT vs. placebo). This analysis revealed no significant relationship between EQ scores and accuracy for the OXT group, b= -0.005, t(63) = -0.29, p > 0.05, but a significant positive relationship for the placebo group b= 0.051, t(63)= 2.64, p= 0.01. As displayed in Figure

3, the group-by-EQ interaction was driven by an increase in accuracy for difficult items among placebo participants with higher EQ scores, whereas EQ had no effect on participants in the OXT group. For easy items, no interaction of group (OXT vs. placebo) and empathy on mentalizing accuracy was observed [$F(1, 63)= 3.67$, $p > 0.05$], and we found no significant relationship between EQ and accuracy neither for the OXT group, $b= -0.02$, $t(63)= -1.15$, $p > 0.05$ nor the placebo group $b= 0.031$, $t(63) = 1.55$, $p > 0.05$.

## 3.4 Discussion

The present study aimed to investigate the effect of OXT on easy and difficult items of the RMET in participants with high and low empathy scores. In line with our hypothesis, we showed that a single dose of intranasally administered OXT enhances mentalizing abilities. This effect was only observed for difficult items. Regarding the question whether the effect of OXT on mentalizing is moderated by individual differences in empathy, we demonstrated that only participants with lower empathy scores benefited from OXT application. Independent of OXT administration, we showed better mentalizing accuracy for difficult items in participants with higher empathy scores. It is important to note that our results cannot be explained by general effects of OXT on mood, wakefulness and calmness since there were no differences between the two experimental groups in the MDBF before and after the task. More importantly, the OXT group and the placebo group did not differ in their EQ scores. This rules out the possibility that the effects are biased by group differences in baseline empathy scores.

Supporting our hypothesis, OXT improved the recognition accuracy during a mentalizing task. Our findings replicate previous studies on the beneficial effect of OXT on mentalizing (Anagnostou et al. 2012; Domes et al. 2007b, Luminet et al. 2011). In line with Domes et al. (2007b), the OXT effect was only found for difficult items. Since the RMET was formerly designed to investigate severe impairments in mentalizing abilities in adults with autism spectrum disorders, the easy items might have not been challenging enough to display the effect of OXT. The effect of OXT on the RMET has previously been demonstrated for both easy (Guastella et al. 2010) and difficult items (Domes et al. 2007b). Notably, the samples in the above-mentioned studies differed in social competence, with autistic adolescents (Guastella et al. 2010) and healthy volunteers (Domes et al. 2007b), respectively. Hence, it seems possible that OXT-

induced effects on mentalizing are most pronounced for tasks that are challenging (e.g. difficult items for healthy participants) but not too difficult (e.g. easy items for autistic participants).

There are several possible explanations for the underlying processes of the observed effects. An essential component of mentalizing is the decoding of social signals such as facial expressions. Our findings replicated previous studies, demonstrating that OXT increased the ability to correctly identify emotional facial expressions in healthy subjects (for a review see van Ijzendoorn and Bakermans-Kranenburg 2012) and clinical samples (Averbeck et al. 2012; Baron-Cohen et al. 2001; Guastella et al. 2010). Alternatively, one might hypothesize that OXT enhances mentalizing by increasing social memory (Domes et al. 2007b). Previous neuroimaging research has suggested that autobiographical memory is an important prerequisite of understanding the mental states of others' (Andrews-Hanna et al. 2014; Cavanna & Trimble, 2006; Gallagher & Frith, 2003). Mentalizing tasks require participants to recall previously stored memories of other persons´ mental states and their corresponding facial expressions and match them to the stimuli presented. A number of studies have demonstrated the potential of OXT as an enhancer for memory processes (Guastella et al. 2008b; Savaskan et al. 2008; Weigand et al. 2013). These studies gain empirical support from neuroanatomical findings, for example OXT receptors have been found in brain circuitries underlying memory processes namely the hippocampus and the septum (Gimpl and Fahrenholz 2001; Meyer-Lindenberg et al. 2011).

Our results regarding the specific effect of OXT in subjects with lower empathy scores support previous work on the variability of OXT effects in social cognition (Bartz et al. 2011b; Olff et al. 2013). An interpretation of this effect might be OXT-induced changes in perceptual salience processing of social cues. Supporting this notion, recent studies showed that OXT increases gaze to the eye region, thus accentuating cues that are highly relevant for interpersonal communication (Andari et al. 2010; Guastella et al. 2008a). Consistent results were found in a recent animal study that reports OXT-induced attention to the eye region in rhesus monkeys (Dal Monte et al. 2014).

Our findings indicate that only those participants who are less attuned to social information (i.e. who are less empathic) benefit from OXT. For those participants it might be more helpful to increase awareness of socially relevant information in the environment, in particular the salience of the eye region in order to correctly identify

mental states of others. On the opposite, OXT had no impact on participants with already high levels of empathy. This explanation is consistent with interactionist views emphasizing that individual differences in competencies interact with situational variables to determine behavior (Mischel and Shoda 1995).

Consistent with the salience hypothesis, recent studies showed that OXT promotes early attentional processes that might facilitate prosocial behavior (Domes et al. 2013b; Schulze et al. 2011). Furthermore, better emotion recognition after OXT administration is associated with increased pupil dilation, suggesting that OXT promotes the allocation of attentional resources during processing of emotionally salient facial expressions (Prehn et al. 2013). The assumption that OXT enhances the salience of social cues also gains considerable support from animal studies. Previous results indicate that OXT modulates the salience of social cues by boosting the dopamine system (Melis et al. 2007; Shahrokh et al. 2010). In humans, Groppe et al. (2013) recently found that OXT enhances activation in the ventral tegmental area (VTA), a brain region rich in OXT receptors (Loup et al. 1991), in response to social cues. The VTA plays a crucial rule in processing the salience of social cues as dopamine neurons project from the VTA to the nucleus accumbens (Bromberg-Martin et al. 2010). In addition to the salience hypothesis, Hurlemann et al. (2010) have shown that OXT application directly enhances empathy. This enhancement might enable subjects with lower empathy scores to correctly identify mental states.

In the placebo but not in the OXT group, we also observed increased performance in participants with high empathy scores for difficult items. This finding is compatible with previous studies investigating the relationship between mentalizing and empathy (Besel and Yuille 2010; Martin et al. 1996). The findings suggest that participants with higher EQ scores are able to identify facial expressions more accurately. Given that facial expression recognition is a prerequisite of mentalizing (Blair 2003), it seems plausible that these participants show better task performance as compared to participants with lower EQ scores.

There are several limitations that are important to consider. First, our study sample only included male participants. Previous studies have reported gender differences in OXT-dependent effects (Domes et al. 2010; Lischke et al. 2012b), indicating that our results might not generalize to women. Future studies should address this issue by investigating both male and female participants. Second, regarding the assessment of

empathy in this sample, it is important to acknowledge the subjectivity of self-reported empathy. Our design would have benefited from a performance-based empathy measurement, for example by including a specific empathy task in the test session.

## 3.5 Conclusion

An important aspect of interpersonal communication is the ability to identify internal mental states of others. We demonstrate that OXT enhances mentalizing using the RMET. However, our data also suggests that OXT does not uniformly facilitate mentalizing in humans. Specifically, OXT improves mentalizing for difficult items only in participants with low ability to empathize. These findings indicate that OXT seems to play a more nuanced role in social cognition and strongly depends on baseline socio-cognitive skills such as empathy.

# 4 Transcranial Direct Current Stimulation Enhances Cognitive Control During Emotion Regulation

Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M (2014) Brain Stimulation 7(1):105-112.

http://dx.doi.org/10.1016/j.brs.2013.08.006

**Abstract**

The ability to cognitively control emotions is critical for mental health. Previous studies have identified the dorsolateral prefrontal cortex (dlPFC) as a core region in cognitive reappraisal. However, there is only scarce evidence whether directly modulating dlPFC activity results in improved capacities for cognitive reappraisal.

In this study, we used anodal transcranial direct current stimulation (tDCS) over the right dlPFC to investigate the effects of increased dlPFC excitability on cognitive reappraisal as indexed by subjective emotional arousal ratings and skin conductance responses.

The study was designed as a double-blind, between-subjects, sham-controlled trial. Half of the healthy participants were randomly assigned to receive either active tDCS (n = 21, 1,5 mA for 20 minutes over the right dlPFC) or sham stimulation (n = 21). Participants viewed negative and neutral pictures from the International Affective Picture System while they were instructed to either downregulate, upregulate or maintain their emotions. After each picture presentation, participants rated the intensity of emotional arousal. Skin conductance responses and gaze fixation were assessed.

Our results revealed that anodal prefrontal tDCS during downregulation resulted in decreased skin conductance responses and decreased emotional arousal ratings. The opposite pattern was observed for the upregulation condition in which anodal tDCS resulted in higher arousal ratings accompanied by marginally enhanced skin conductance responses

Our data indicates that tDCS facilitates cognitive reappraisal in both directions by either increasing or decreasing emotional responsiveness depending on the regulatory goal. This provides further evidence for the potential use of tDCS as a tool to modulate cognitive reappraisal. However, given the limitations of the present study, our findings need to be replicated and complimented by further studies.

## 4.1 Introduction

The ability to cognitively control emotional experiences is an important predictor for mental health (Gross and John 2003). While emotions are helpful in facilitating goal-directed behavioral responses (Davidson et al. 2003b), they can also be maladaptive, if they happen at an inappropriate time or at a wrong intensity level (Gross and Thompson 2007). In the latter case emotions need to be controlled using emotion regulation strategies. According to Thompson (1994), emotion regulation can be defined as: "extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features, to accomplish one's goals" (p. 28).
Research on emotion regulation has suggested different ways of modulating emotional experiences ranging from attentional control to cognitive change (Ochsner and Gross 2005). The present study focuses on cognitive reappraisal as a form of cognitive change. This type of emotion regulation refers to changing the way one appraises a situation in order to change its emotional impact. In studies investigating cognitive reappraisal, subjects are typically trained with cognitive reappraisal strategies to down-or upregulate negative emotions elicited by pictures or videos.

A number of studies in recent years have investigated how cognitive reappraisal impacts neural responses to emotional stimuli. (Eippert et al. 2007; Kanske et al 2011; Ochner et al. 2004; Urry et al. 2009). These studies have identified a network of brain regions that are engaged while attempting to reappraise negative emotions. Specifically, it has consistenly been shown that the dorsolateral prefrontal cortex (dlPFC) plays a crucial role in that process. For example, Eippert et al. (2007) and Ochsner et al. (2004) found that both down- and upregulation of negative pictures activated the dlPFC as compared to a control condition. Prior imaging studies have shown that increased dlPFC activation is associated with altered amygdala activation during cognitive reappraisal. This results in decreased amygdala activity during downregulation and increased activation during upregulation of negative emotions (Ochsner et al. 2004). Another study by Wager et al. (2008) reported a mediation analysis that provided evidence for prefrontal involvement in generation and regulation of emotional states through different subcortical pathways.

Emotional stimuli induce not only changes in the brain but also autonomic changes such as skin conductance responses (SCR, Dawson et al. 2000). Changes in skin conductance responses have been proven as a sensitive and reliable measure of emotional arousal with larger SCR usually observed for highly arousing stimuli. Most importantly, there is substantial evidence for a neuroanatomical basis for correspondence between the amygdala-frontal circuit and changes in SCR (Critchley 2009). For example, Mangina et al. (1996) was able to demonstrate that electrical stimulation of the amygdala strongly modulated SCR.

One well established way to investigate emotional states is by the means of the valence-arousal model (Frijda 1986; Lang 1995). In this model, emotional states are constituted by the two dimension: valence (pleasantness) and arousal (physical activation). In the present study, we used one dimension, namely arousal, to measure the success of implementing cognitive reappraisal strategies for downregulation and upregulation of negative emotions. Our rationale for choosing SCR to investigate reappraisal success is in line with several previous studies, which used IAPS pictures in an emotion regulation tasks. Increased SCR is observed when participants upregulate emotions as compared to downregulation. (Driscoll et al. 2009; Eippert et al. 2007, Kim and Hamann 2012). To our knowledge, only one study by Urry et al. (2009) has demonstrated that attempts to downregulate negative emotions are associated with decreased SCR as compared to a control condition.

Given the growing body of neurobiological evidence about the mechanisms of emotion regulation and its importance for mental and physiological health (Berking and Wupperman 2012), the question arises how emotion regulation can be improved. Previous studies have demonstrated the effectiveness for antidepressant treatment (Heller et al. 2013), emotion regulation group trainings (Schuppert et al. 2009), and mindfulness-based stress reduction trainings (Goldin and Gross 2010) for improving emotion regulation on a subjective and neural level.

As mentioned above, there is substantial evidence for the role of dlPFC during cognitive reappraisal of negative emotions from brain imaging studies. However, these are only correlational and only very few studies have investigated causal mechanisms between dlPFC activation and emotion regulation processes. tDCS is an emerging brain stimulation technique that can be used for addressing the question of causality.

During tDCS, a continous weak electrical current is applied through two electrodes positioned over the participant´s scalp surface. It induces transient, stimulation polarity-dependent excitability shifts of the human cortex via neuronal de- or hyperpolarization (Miranda et al. 2006). Specifically, anodal tDCS results in increased cortical excitability, whereas cathodal tDCS decreases it (Nitsche and Paulus 2000). Empirically it has been shown that anodal tDCS of the dlPFC is associated with working memory enhancement and improvement in other cognitive domains (Andrews et al. 2011; Dockery et al. 2009; Fecteau et al. 2007; Fregni et al. 2005; Kincses et al. 2004).

Despite the initial promise of tDCS effects in enhancing cognitive functioning, little attention has been paid so far to investigate emotional processing. Recent work by Peña-Gómez et al. (2011) has proposed that tDCS over the dlPFC reduces the perceived degree of emotional valence for negative IAPS pictures. The authors explained this effect by a tDCS induced enhancement of cognitive control over emotional experience. In line with these results, Boggio et al. (2009) reported that prefrontal tDCS resulted in decreased discomfort ratings during the presentation of images depicting human pain. Another recent study investigated the effects of tDCS on cognitive control (Wolkenstein and Plewnia 2013). The authors found that active tDCS over the dlPFC ameliorated cognitive control for emotional information in healthy volunteers.

Interestingly, a growing body of findings indicates that the effects of brain stimulation on task performance strongly depend on the level of neuronal activity at the time of stimulation (Silvanto et al. 2008). The importance of state-dependent stimulation effects has been illustrated in transcranial magnetic stimulation (TMS) studies investigating perceptual and cognitive processes. In these studies, the functional state of the cortex prior to the stimulation was manipulated by means of adaptation with a stimulus or a category used in the task which altered the task performance (Cattaneo et al. 2010a; Cattaneo et al. 2010b; Kadosh et al. 2010). Furthermore, it has been shown that tDCS effects on functional connectivity in verbal fluency and deactivation of task-related networks differed depending on the specific subcomponents of the task (Pereira et al. 2013). Taken together, these findings are in line with our assumption that tDCS induced changes in emotion regulation might depend on the respective reappraisal condition.

However, it is important to note that the previous mentioned studies on emotional processing and cognitive control did not use a specific emotion regulation task (i.e., no standardized cognitive reappraisal instructions were given). Therefore, their findings

cannot be directly associated with the improvement of emotion regulation abilities induced by tDCS. Another limitation of previous studies is that they did not control for visual attentional deployment during the task. As highlighted by van Reekum et al. (2007) cognitive reappraisal and attentional deployment can both contribute to changes in emotional response during cognitive reappraisal. Specifically, it has been shown that participants show different gaze fixation patterns towards emotional stimuli depending on their regulation goal. Regarding our study, it is necessary to assess gaze fixation for two reason. First, we aimed at ruling out the possibility that the two experimental groups differ in the way they visually scan the IAPS pictures. Second, given the lack of control whether the participants are actually engaged in the task, we could confirm that participants were following the instruction to look at the pictures throughout the experiment.

It is important to note that most of the above mentioned tDCS studies on emotional processing chose the left dlPFC for stimulation. Nevertheless, in the present study we decided to stimulate the right dlPFC. Our rationale for chosing this stimulation site was twofold. First, we considered the valence theory of side-lateralized activity of the prefrontal cortex during emotional processing (Davidson 1992; Davidson 1999). It has been suggested that positive emotional information is preferentially processed in the left hemisphere whereas the processing of negative emotional information is lateralized in the right hemisphere. This notion is further supported by brain simulation studies investigating the right dlPFC (Baeken et al. 2010; Leyman et al. 2008). Since our emotional stimulus material contained negative IAPS pictures only, we decided for the right dlPFC. Second, our decision derived from the results of neuroimaging studies on emotion regulation. A recent review by Ochsner et al. (2012) on functional imaging studies of emotion indicated that the right dlPFC is involved in down-regulation and up-regulation of emotional states. They propose the following explanation for this pattern of results: Previous studies have reported that the right dlPFC is involved in the selection and inhibition of various kinds of responses (Aron et al. 2004; Lieberman 2007b). Thus, the right dlPFC might play a role in deliberately selecting a new stimulus-appropriate reappraisal in favor of one´s initial appraisal of that stimulus. This in turn might alter subcortical activation.

Based on the above mentioned findings regarding the neural circuitry underlying emotion regulation and the proven capacity of tDCS to enhance cognitive functioning, we aimed to investigate tDCS as a tool to improve emotion regulation.

Our study had two main objectives: The first aim was to investigate whether a single session of tDCS applied over the right dlPFC would modulate emotional arousal ratings while participants attempted to reappraise negative pictures. We hypothesized that arousal ratings would be decreased during the downregulation condition and increased during the upregulation condition during anodal tDCS as compared to sham stimulation. Secondly, we aimed to evaluate the effect of tDCS on autonomic responses as indexed by SCR during cognitive reappraisal. According to the findings by Urry et al. (2009), we hypothesized that under tDCS, attempts to downregulate negative emotions would lead to decreased SCR whereas attempts to upregulate would be associated with increased SCR as compared to the sham condition.

To test these predictions, we used a study design that crosses factors for cognitive reappraisal type (downregulation, upregulation, negative maintain, neutral maintain) with tDCS application type (active, sham).

## 4.2 Methods and material

### 4.2.1 Subjects

48 subjects (25 women, 23 men), aged between 20 and 47 years (mean age= 29.8, SD= 6.2) participated in this study. All subjects were screened for psychiatric disorders using the short version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, SCID) (Wittchen et al. 1997). Subjects with any history of psychiatric or neurological desease or implanted metal objects were excluded from the study. All subjects were naïv to tDCS, the emotion regulation task and the hypotheses of the study. Written consent was obtained and subjects were paid for their participation. The study was approved by the local ethics commitee of the Department of Psychiatry Charité-Universitätsmedizin, Campus Benjamin Franklin, Berlin.

### 4.2.2 Experimental design

The study was designed as a double-blind, between-subjects, sham-controlled trial that took place on two separate days. We chose a between-subjects design for practical

reasons and in order to avoid learning effects that might occur after repeated practice of reappraisal strategies in subsequent experimental sessions. Previous studies also using emotion regulation trainings showed that reappraisal strategies can be successfully acquired by repeated training opportunities (Schuppert et al. 2009; Woud et al. 2012). To ensure that our results are not influenced by training effects and better performance after repeated training opportunities, we decided to have only one test session in addition to the training session. Half of the subjects were randomly assigned to receive either active anodal stimulation (n = 23) or sham stimulation (n = 25).

On the first day, the subjects received an extensive training to acquaint them with the use of cognitive reappraisal strategies. The experimenter provided them with detailed standardized instructions and reappraisal examples for the different regulation instructions (downregulation, upregulation, negative maintain, neutral maintain). At the end of the training, all subjects were able to generate appropriate reappraisals that followed our reappraisal instructions. The actual testing session took place three to four days later. Before the testing session, participants conducted six practice trials. Picture stimuli used in the training session and in the practice trials were different from those used in the experimental session.

### 4.2.3 Reappraisal task

The reappraisal task consisted of four conditions: downregulate negative emotions, upregulate negative emotions, maintain negative emotions, maintain neutral emotions. We adapted the reappraisal instruction from Ochsner et al. (2004). For downregulation participants attempted to view the scene objectively from a third-person perspective (i.e., a doctor) who is not involved in the scene or to imagine a better outcome of the situation than the one depicted. Accordingly, for upregulation participants were instructed to imagine that the event in the picture happened to a beloved one or to imagine that the outcome of the scene is worse than the one displayed in the picture. In maintain trials participants were instructed to maintain their emotional experience without trying to modify it using reappraisal strategies.

### 4.2.4 Stimuli and trial structure

In the task, participants were presented with 72 negative and 24 neutral pictures taken from the IAPS[1] (Lang et al. 2001). Three sets of 24 negative IAPS pictures were

randomly assigned to the three regulation conditions (negative downregulate, negative upregulate or negative maintain). Neutral pictures were only presented in the neutral maintain condition. The negative picture sets were matched according to valence and arousal of the IAPS norm ratings (all $p > 0.05$). The neutral picture set had higher valence ($p < 0.05$), and lower arousal ratings ($p < 0.05$) than the negative sets. Pictures were presented using the experimental control software Presentation (Neurobehavioral Systems Inc., Albany, CA). Each trial started with a cue indicating the regulation condition (downregulate, up-regulate, or maintain) which was presented for 1 s. Afterwards, the IAPS picture was presented for 8 s. The order of the regulation conditions was counterbalanced. The participants were instructed to maintain implementing the cued regulation strategy during the total time of picture presentation. After presentation of each picture, participants rated the intensity of arousal evoked by the picture on a nine-point scale (1=very low arousal, 9= very high arousal). An example trial of the task is illustrated in Figure 9.

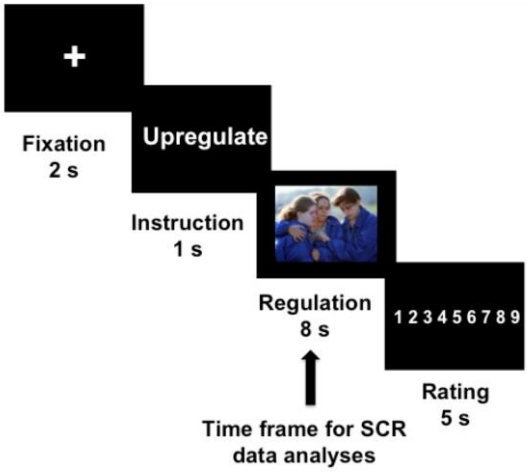


**Fig. 9**

Trial structure for the cognitive reappraisal task. Each trial consisted of four phases: a 2 s fixation cross, a 1 s instruction (downregulate, upregulate, negative maintain, neutral maintain), a 8 s picture display and a 5 s rating phase; SCR= skin conductance response.

[1] The following IAPS pictures, listed by catalog number, were used:

2375, 2520, 2661, 2683, 2691, 2703, 2704, 2718, 2730, 2753, 2800, 3005, 3015, 3016, 3017, 3022, 3051, 3053, 3071, 3150, 3180, 3191, 3215, 3225, 3250, 3280, 3302, 3350, 3500, 3530, 5500, 5510, 5530, 5533, 6213, 6243, 6312, 6313, 6314, 6315, 6350, 6510, 6550, 6555, 6560, 6562, 6571, 6821, 6825, 6831, 6834, 6838, 7000, 7002, 7004, 7009, 7010, 7041, 7057, 7080, 7090, 7095, 7100, 7130, 7140, 7190, 7217, 7234, 7235, 7490, 7700, 7710, 8230, 8231, 8480, 9040, 9042, 9102, 9252, 9253, 9265, 9341, 9400, 9410, 9415, 9419, 9420, 9424, 9426, 9428, 9430, 9433, 9452, 9520, 9910, 9920.

### 4.2.5 Control variables

To ensure group matching the following questionnaires were completed by all participants after testing: The Emotion Regulation Questionnaire (ERQ), (Gross and John 2003) the Toronto Alexithymia Scale (TAS-20), (Parker et al. 2003) and the NEO Five-Factor Inventory (NEO-FFI), (Costa 1992). To control for mood changes, the Multidimensional State Questionnaire (MDBF) (51) was completed before and after the experimental session.

### 4.2.6 Transcranial direct current stimulation

tDCS was applied through a pair of saline-soaked surface sponge electrodes (anodal electrode surface= 35 $cm^2$, cathodal electrode surface= 100 $cm^2$) connected to a battery-driven constant current stimulator (DC-Stimulator, NeuroConn GmbH, Ilmenau, Germany). For anodal stimulation of the right dlPFC, the anode electrode was placed over F4 according to the 10-20 international system for EEG electrode placement. The cathode was placed above the left supraorbital region at least 5 cm from the anode (Miranda et al. 2006). A relatively large reference electrode was used to rule out the possibility that the observed effect emerged from supraorbital stimulation.
During active stimulation a constant current of 1,5 mA was applied for 20 minutes. The sham condition consisted of 30 seconds of stimulation, afterwards the stimulator was turned off. The subjects felt the initial itching in both of the stimulation conditions and were thus unable to recognize the stimulation condition. The tDCS device contained a study mode for double-blind trials. Prior to the start of the study, a colleague who was not involved in the study generated numeric codes for active and sham tDCS stimulation sessions which were assigned to the subjects. At the beginning of each test session, the experimenter entered the preassigned code for each subject, and thus was completely unaware of the stimulation condition to follow. The stimulation was applied during the emotion regulation task and started 4 minutes before the task. The impedance was controlled by the device, normally ranging below 5 kΩ.

### 4.2.7 Recording and analysis of Skin Conductance and Eye Tracking data

SCR was recorded continously during the emotion regulation task with a sampling rate of 40 Hz using a biofeedback sampling device (Biofeedback $2000^{X\text{-}pert}$, Schuhfried GmbH, Austria). The electrode was connected to the ring finger of the left hand. SCR data was

analyzed using the MATLAB 7.11.1 (Mathworks Inc., Sherborn, MA) based software LedaLab version 3.3.1 (www.ledalab.de). Within the 8 s of picture presentation, SCR was decomposed by continous decomposition analysis (CDA) (Benedek and Kaernbach 2010). This method extracts the phasic information underlying the skin conductance response, and aims at retrieving the signal characteristics of the underlying sudomotor nerve activity.

Gaze fixation was measured using an iView X system (SensoMotoric Instruments, Teltow, Germany). Before the start of the experiment, gaze fixations were calibrated by instructing the participants to look at each of 4 dots presented in a random order in either one of the four corners of the computer screen. Gaze fixation was measured at 60 Hz. For further analysis, the amount of time participants fixated pre-defined areas of interest within one picture was calculated. To define the areas of interest, a template was created by drawing elliptical areas on each picture using Adobe Photoshop CS6 (Adobe Systems Inc., CA). An area of interest was defined as only those details that provide emotional meaning to the scene depicted in the picture. Eye tracking data was analyzed using the MATLAB based software Gazealyze version 0.90b (www.gazealyze.sourgeforge.net).

### 4.2.8 Statistical analysis

Subjective arousal ratings, SCR variables and gaze fixation variables were analyzed using repeated measures analyses of variance (ANOVAs) to test for main effects and interactions with the within-subjects factors Regulation Condition (downregulation, upregulation, negative maintain, neutral maintain) and the between-subjects factors Stimulation (active, sham). Further statistical analyses were conducted using t-test comparisons. (active vs sham stimulation). Paired-samples t-tests were used to compare the different regulation conditons within each experimental group. Greenhouse–Geisser corrections were applied where appropriate. All tests were two-tailed and the significant threshold was set at a probability of $p \leq 0.05$. Statistical analyses were carried out using PASW (Predicitive Analysis SoftWare, Version 18.0, Chicago: SPSS Inc., Illinois, USA).

## 4.3 Results

### 4.3.1 Demographics and individual characteristics

Data from six subjects were exluded from analyses because they failed to produce detectable SCR amplitudes. The final sample size was 42 (n= 21 active tDCS; 11 women and n= 21 sham tDCS; 11 women). There were no significant differences (all ps > 0.05) between participants in the two experimental groups (active vs sham stimulation) with respect to age, habitual use of emotion regulation strategies (ERQ), the subscales of the NEO-FFI questionnaire and alexithymia scores (TAS). The characteristics of the two experimental groups are reported in Table 3.

| | | active tDCS M (SD) | sham tDCS M (SD) | t | p value |
|---|---|---|---|---|---|
| **age** | | 28.4 (6.9) | 28.5 (6.4) | 0.046 | .963 |
| **ERQ** | Reappraisal | 31.2 (4.8) | 31.8 (5.3) | 0.366 | .716 |
| | Suppression | 11.5 (2.9) | 11.3 (3.9) | -0.180 | .858 |
| **NEO-FFI** | Neuroticism | 16.5 (6.3) | 18.2 (6.9) | 0.816 | .419 |
| | Extraversion | 30.6 (6.2) | 29.6 (5.9) | -0.511 | .612 |
| | Openness | 37.6 (6.1) | 36.9 (4.0) | -0.450 | .655 |
| | Agreeableness | 34.8 (4.1) | 34.4 (5.9) | -0.244 | .808 |
| | Conscientiousness | 33.8 (3.8) | 32.1 (6.3) | -1.039 | .305 |
| **TAS** | Difficulty Identifying feelings | 11.0 (3.1) | 11.4 (2.6) | 0.434 | .666 |
| | Difficulty Describing feelings | 9.5 (3.2) | 9.3 (2.8) | -0.208 | .837 |
| | Externally Oriented thinking | 13.9 (3.7) | 15.2 (3.1) | 1.283 | .207 |
| **MDBF pre** | Elevated vs. Depressed mood | 16.4 (2.5) | 15.4 (3.0) | -1.11 | .273 |
| | Wakefulness vs. Sleepiness | 14.2 (3.7) | 13.5 (4.0) | -0.596 | .554 |
| | Calmness vs. Restlessness | 16.3 (3.4) | 15.1 (3.1) | -1.186 | .243 |
| **MDBF post** | Elevated vs. Depressed mood | 15.1 (3.4) | 14.2 (3.6) | -0.887 | .380 |
| | Wakefulness vs. Sleepiness | 13.1 (3.8) | 12.0 (2.9) | -1.091 | .282 |
| | Calmness vs. Restlessness | 15.3 (3.1) | 14.9 (2.9) | -0.206 | .838 |

**Tab. 3**

Demographics and individual characteristics. M mean, SD standard deviation, ERQ Emotion Regulation Questionnaire, NEO-FFI Neo Five-Factor Inventory, TAS Toronto Alexithymia Scale, MDBF Multidimensional State Questionnaire. t t-value from independent samples t-test, two-tailed

### 4.3.2 Effects of tDCS on emotional ratings

tDCS was well tolerated by all subjects and all subjects completed the entire experiment. The only side effect mentioned by the participants was an initial itching sensation. No skin lesions or headaches were reported after the end of the session.

First, we analyzed the effect of tDCS on participant´s emotional state as measured by three subscales of the MDBF before and after the task. The ANOVA (Stimulation x Time x MDBF subscales) revealed a main effect of Time on emotional state [$F(1,80)= 6.72$, $p= .013$]. Further t-tests demonstrated that participants reported increased depressed mood at the end of an experimental session ($t= 2.28$, $p = .028$). Importantly, we observed no main effect for Stimulation on emotional state [$F(1,40)= 1.60$, $p= .213$] nor a significant interaction for the factors Stimulation, Time and MDBF subscales [$F(2,80)= .52$, $p= .599$].

Regarding the influence of tDCS on emotional arousal ratings, we observed a main effect of Regulation Condition [$F(3,120)= 211.23$, $p < .001$] and an interaction of Stimulation and Regulation Condition [$F(3,120)= 18.13$ $p < .001$]. Further t-tests revealed lower arousal ratings in the downregulation condition for the active stimulation group ($M= 2.17$, $SD= .88$) as compared to the sham stimulation group ($M= 3.46$, $SD= .71$; $t= 5.22$, $p < .001$). Higher arousal ratings in the upregulation condition were found for the active stimulation group ($M= 6.08$, $SD= .59$) as compared to the sham stimulation group ($M= 4.86$, $SD= .83$; $t= -5.50$, $p < .001$). Furthermore we found lower arousal ratings in the negative maintain condition for the active stimulation group ($M= 3.50$, $SD= 1.27$) as compared to the sham stimulation group ($M= 4.24$, $SD= .82$; $t= 2.25$, $p = .03$; only a trend because of Bonferroni correction; adjusted p value = 0.008).

In the next step we analyzed differences within the active stimulation group and the sham stimulation group between the different reappraisal conditions. For the sham stimulation group, paired t-tests revealed lower arousal ratings for the downregulation condition as compared to the negative maintain condition ($t = -5.17$, $p < .001$). The

difference between the downregulation condition and the upregulation condition was also significant (t = 5.11, p < .001).

For the active stimulation condition we observed lower arousal ratings for the downregulation condition as compared to the negative maintain condition (t = -4.02, p < .001) and higher arousal ratings for the upregulation condition as compared to the negative maintain condition (t = 8.26, p < .001). The difference between the downregulation condition and the upregulation condition was also significant (t = 14.99, p < .001). The results for the arousal ratings are illustrated in Figure 10.

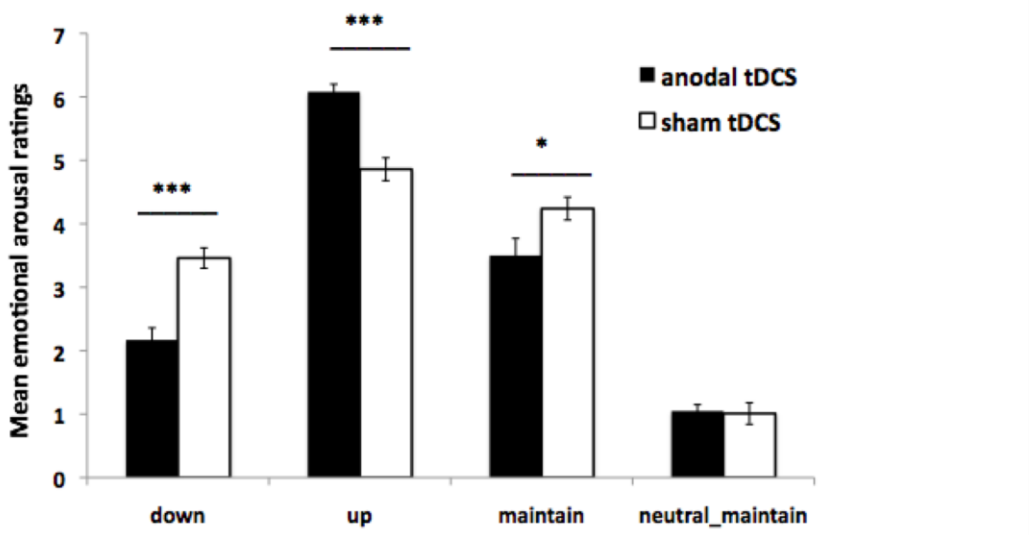


**Fig. 10**

Mean emotional arousal ratings for both groups (anodal tDCS or sham tDCS) and reappraisal condition (downregulate, upregulate, negative maintain, neutral maintain). * indicate significant post-hoc comparisons (*** p < 0.001; * p < 0.05). Bars represent standard errors (SE).

### 4.3.3 Effects of tDCS on SCR

Regarding the influence of tDCS on SCR, we observed a main effect of Regulation Condition [F(3,120)= 39.27, p < .001] and an interaction of Stimulation and Regulation Condition [F(3,120)= 6.10 p= .001]. Further t-tests demonstrated that these effects were driven by lower SCR in the downregulation condition for the active stimulation group (M= .26, SD= .27) as compared to the sham stimulation group (M= .56, SD= .36; t= 3.05, p = .004). Higher SCR in the upregulation condition was found for the active stimulation group (M= 1.27, SD= .36) as compared to the sham stimulation group (M= .99, SD= .29;

t= -2.69, p = .01; only a trend because of Bonferroni correction; adjusted p value = 0.008).

In the next step we again report the statistics of the within group comparisons between the different reappraisal conditions. For the sham stimulation group, paired t tests only revealed lower SCR for the downregulation condition as compared to the upregulation condition (t = 3.71, p = .001).

For the active stimulation condition we observed lower SCR for the downregulation condition as compared to the negative maintain condition (t = -4.18, p < .001) and higher SCR for the upregulation condition as compared to the negative maintain condition (t= 5.36, p < .001). The difference between the downregulation condition and the upregulation condition was also significant (t= 13.70, p < .001). The SCR results are illustrated in Figure 11.

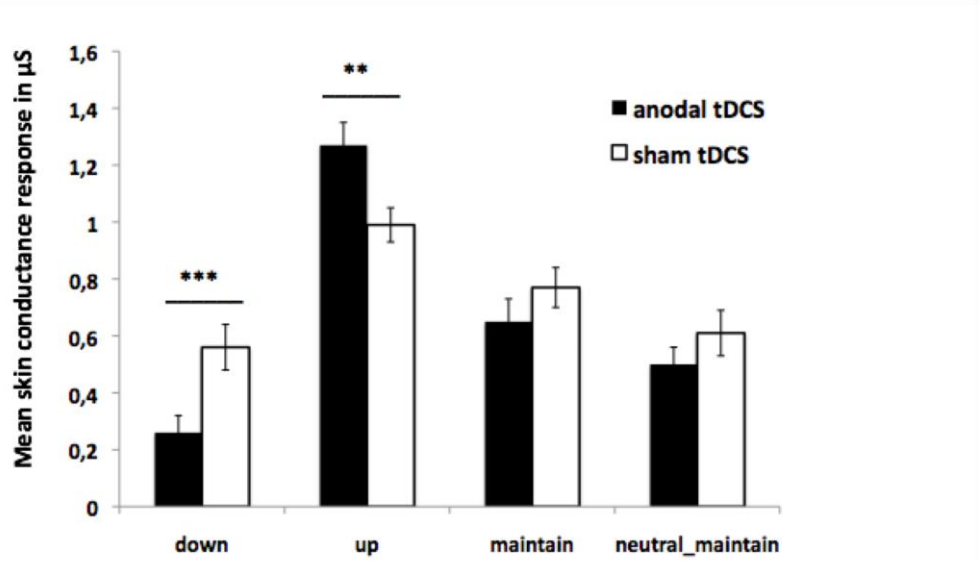


**Fig. 11**

Mean skin conductance response (in µS) for both groups (anodal tDCS or sham tDCS) and reappraisal condition (downregulate, upregulate, negative maintain, neutral maintain). * indicate significant post-hoc comparisons (*** p < 0.001; ** p < 0.01). Bars represent standard errors (SE).

### 4.3.4 Differences in gaze fixation

The ANOVA revealed a main effect of Regulation Condition [$F(3,120)= 58.91$, $p < .001$]. Further t-tests demonstrated that all participants spend less time fixating emotional relevant parts of the picture when instructed to downregulate as compared to the negative maintain condition (downregulate: $M= 3.4$, $SD= .56$; negative maintain: $M= 4.1$, $SD= .44$; $t= -7.67$, $p < .001$). In addition, the time spent on relevant parts of the image was longer for the upregulation condition as compared to the negative maintain condition (upregulate: $M= 5.0$, $SD= .59$; negative maintain: $M= 4.1$, $SD= .44$; $t= 17.40$, $p < .001$). No main effect of Stimulation [$F(1,38)= .24$, $p= .63$] nor an interaction of Regulation Condition and Stimulation [$F(3,120)= .83$, $p= .48$] was observed. The gaze fixation results are illustrated in Figure 12.

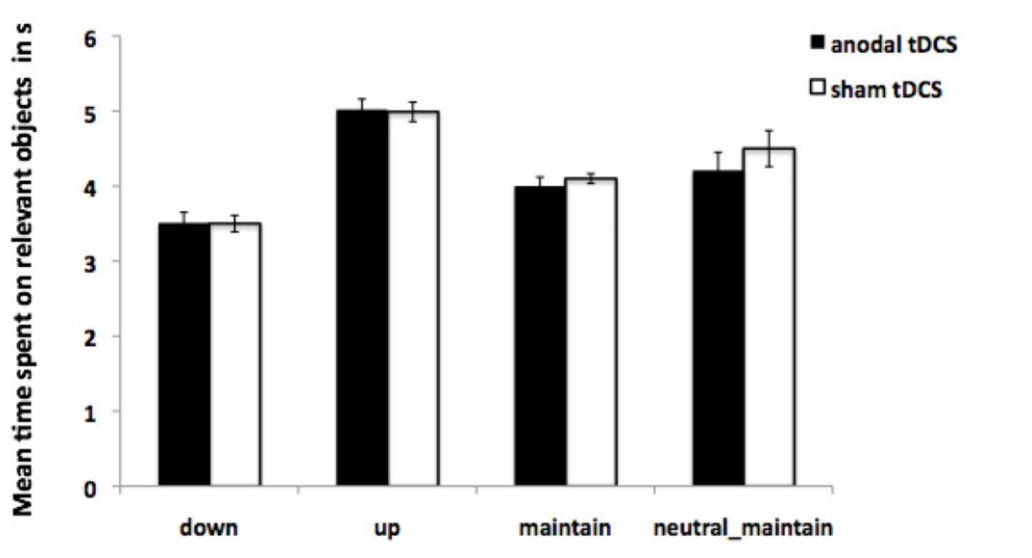


**Fig. 12**

Mean time (in s) spent fixating the relevant objects that rendered the image negative in valence for both groups (anodal tDCS or sham tDCS) and reappraisal condition (downregulate, upregulate, negative maintain, neutral maintain). Bars represent standard errors (SE).

## 4.4 Discussion

The aim of this study was to investigate the effects of right dlPFC stimulation on cognitive reappraisal. We observed that anodal tDCS over the right dlPFC during

downregulation resulted in lower arousal ratings and decreased skin conductance responses. The opposite pattern was observed for the upregulation condition in which anodal tDCS resulted in higher arousal ratings accompanied by marginally enhanced skin conductance responses. The results of the within-group comparisons suggest that the differences between the regulation conditions (downregulate vs negative maintain and upregulate vs negative maintain) were more pronounced in the active tDCS group. This supports the notion that subjects in the active tDCS condition were more capable of reappraising negative emotions.

An additional analysis of gaze fixation showed differences between the reappraisal conditions but no effect of stimulation. To summarize, these results indicate that anodal tDCS facilitated cognitive reappraisal in both directions. Depending on the reappraisal condition (downregulation or upregulation) emotional arousal was either elevated or reduced. These findings are consistent with the idea of state-dependency. Specifically, differential responses to tDCS seem to depend on the particular reappraisal process the participants are performing.

This pattern of results also supports current models of cognitive-affective brain circuits underlying cognitive reappraisal (for a review see Ochsner and Gross 2005). Based on these findings, a potential explanation for the observed effects might be that tDCS impacts the level of cortical excitability by increasing the firing rate of neurons in the right dlPFC.

Accordingly, increased dlPFC activity might impact autonomic arousal by modulating the neural activity of subcortical structures such as the amygdala. Several lines of evidence have suggested that both down- and upregulating negative emotions are associated with increased dlPFC activity (Eippert et al. 2007; Ochsner et al. 2004). Moreover, connectivity within subcortical-prefrontal circuitry has been shown during cognitive reappraisal (Banks et al. 2007). Another study investigated pathways linking prefrontal acitivity with reappraisal success. They reported two seperable pathways: one leading through the ventral striatum, which may generate positive reappraisals, and another one through the amygdala which may generate negative reappraisals (Wager et al. 2008).

Note that the dlPFC does not directly impact emotion-related amygdala activity, since there is no direct connection between both brain regions. One plausible route is via the

ventromedial prefrontal cortex (vmPFC), which is directly connected to both the dlPFC and the amygdala (Hartley et al. 2010; Price 2005).

Our results are in line with findings by Urry et al. (2009) who reported reappraisal-related changes in SCR during an emotion regulation task (upregulate > negative maintain > downregulate). Furthermore they reported that these effects were mediated by the right amygdala. However, only one study so far has reported tDCS induced changes in autonomic arousal during emotion processing (Brunoni et al. 2013). The authors found that tDCS induced top-down effects under anodal dlPFC stimulation lead to a downregulation of salivary cortisol levels.

We also found a group difference in the negative maintain condition. Specifically, participants in the anodal tDCS group reported lower emotional arousal for negative pictures in the maintain condition compared to the sham tDCS group. This finding opens up the question, whether the two experimental groups differed in basic emotional processing. As indicated by the results of the psychometric tests, the groups did not differ in emotion processing and regulation in general (assessed with the ERQ, TAS-20, NEO-FFI, see 'Demographics and individual characteristics' section). Therefore, we believe that anodal tDCS has also enhanced the participants' automatic tendency to downregulate their emotional responses to negative pictures without having an explicit instruction to do so. When explicitly instructed to up- and downregulate their emotional response, participants even showed greater differences in comparison to the sham group. Importantly, participants in the anodal tDCS group reported higher emotional arousal in the upregulation condition than participants in the sham groups, a difference that goes in the opposite direction than the difference in the maintain condition. The result of higher arousal ratings in the upregulation condition would not have been occurred if groups just differed in basic emotional processing.

Therefore it is very unlikely that the difference in the maintain condition has influenced our results in general. It should also be noticed, that the difference between the groups in the negative maintain condition is only a trend because of Bonferroni correction.

Taken together, our findings suggest that increasing dlPFC activity by tDCS does facilitate emotion regulation as indexed by changes in SCR and subjective arousal ratings depending on the reappraisal condition. Thereby, the data extends findings from previous studies (Boggio et al. 2009; Maeoka et al. 2012; Peña-Gómez et al. 2011) which

demostrated tDCS induced changes in the processing of affective pictures without using an explicit emotion regulation task including cognitive reappraisal strategies.

A considerable strength of this study is the inclusion of gaze fixation analysis to control for attentional deployment during the task. Our results replicate previous findings by van Reekum et al. (2007) who showed that the amount of time participants spent fixating relevant part of the picture changed as a function of the regulatory goal .

Specifically, independent of tDCS application, we observed that participants spend less time on emotionally relevant parts of the picture when attempting to downregulate negative emotions as opposed to spending more time on relevant parts when attempting to upregulate negative emotions. However, our study revealed no differences in gaze fixation patterns between the anodal and sham stimulation group. Therefore, we conclude that the observed differences in arousal ratings and SCR between the groups do not reflect changes in attentional deployment but rather underly modulations of cognitive reappraisal processes.

The lack of tDCS induced mood changes is consistent with previous work. Whereas a study performed by Lippold and Redfearn (1964) proposed a polarity dependent mood effect for healthy subjects, recent studies could not replicate these findings (Koenigs et al. 2009; Plazier et al. 2012; Nitsche et al. 2012).

In the present study we used a between-subject design to investigate tDCS induced changes on emotion regulation. Consequently, it was important to match the two experimental groups on their general abilities to regulate emotions. We addressed this issue by administering the ERQ to measure individual differences in the habitual use of cognitive reappraisal. Importantly, we observed no difference between the participants in the active tDCS group compared to the sham tDCS group regarding the use of reappraisal strategies. Additionally, we tested for group differences in personality traits such as alexithymia, neuroticism, and extraversion that are likely to modulate emotion regulation success (Bermond et al. 2010; Peña-Gómez et al. 2011; Venta et al. 2013). Again, there was no difference in these personality traits between the groups. However, the present study did not contain a baseline measurement prior to the task to measure differences in basic emotional processing and the ability to implement the instructed reappraisal strategies. The lack of baseline measurement might weaken the specificity of our results and therefore the results should be treated with caution.

The ability to modulate ones emotional state is an important cognitive control process skill for humans. For instance, studies have suggested a link between the habitual use of reappraisal strategies and positive psychosocial outcomes (Fehlinger et al. 2013; Gross 2002). On the other hand, recent studies suggested that dysfunctional emotion regulation abilities are important for the development and maintenance of various forms of mental disorders such as depression (Brockmeyer et al. 2012), anxiety disorder (Blair et al. 2012), borderline personality disorder (Glenn et al. 2009), and eating disorder (Svaldi et al. 2012). Given the importance for emotion regulation in mental health, the findings of the present study may have interesting implications for clinical approaches. For example, the efficacy of tDCS in modulating cognitive-emotional circuits of emotion regulation could be used to augment the clinical benefits of cognitive behavioral therapies targeting dysfunctional emotion regulation. Our findings should encourage future studies to investigate the potential use of tDCS to facilitate emotion regulation in clinical samples, such as depression and anxiety disorder.

## 4.5 Limitations

There are certain limitation to this study that are important to consider. First, an additional active stimulation site would have improved the specificity of the results. With the present study design we cannot answer the question if stimulation of any other brain region besides the dlPFC would have resulted in similar effects. Future studies should continue investigating the effect of tDCS in modulating other brain regions related to cognitive reappraisal. Second, we did not include an additional control task to investigate the possible effects of tDCS on other cognitive domains such as working memory or executive functioning. However, from literature it is known that cognitive reappraisal is among the most cognitively complex strategies that involves a number of cognitive processes such as selective attention, working memory, performance monitoring, selecting and inhibiting responses (Ochsner et al. 2012). Given the role of the dlPFC in working memory and attention processes (Curtis et al. 2003; Wager et al. 2004) however, it seems plausible that the effect of tDCS shown in our study is not specific to cognitive reappraisal but also be contributed to an enhancement in other cognitive domains.

Third, because tDCS is a technique that changes brain activity in two areas (under the anode and cathode electrode) one may argue that cathodal stimulation of the right

supraorbital area might be responsible for the observed effects. For example, several neuroimaging studies have identified a network of cognitive reappraisal that also comprises the orbitofrontal cortex (Ochsner and Gross 2005). We did not directly control for that possible confound by including a control condition (e.g. anodal stimulation over the occipital cortex and cathodal stimulation over the supraorbital cortex). However, we addressed this problem by using a large cathode electrode (10 X 10 $cm^{2)}$. Using a very large electrode should result in functionally unipolar tDCS, which has been demonstrated to be by Nitsche et al. (2007). Fourth, we also cannot rule out the possibility that increasing the excitability of the dlPFC activity may also have modulated the response of other nearby located brain regions. Given the complexity of the emotional regulation network, further brain imaging studies are needed to elucidade the role of tDCS in modulating cognitive reappraisal.

## 4.6 Conclusion

The present study shows that the application of prefrontal tDCS enhances cognitive control during the reappraisal of negative emotions. By showing a relationship between prefrontal tDCS and reappraisal success, our results specifically confirm and expand the role of the dlPFC as an important part of the emotional regulatory circuit. Given the limitations of the present study mentioned above, our findings, however, need to be replicated and complimented by further studies. Nevertheless, these results may open up new possibilities for the use of tDCS as an add-on treatment in patients showing dysfunctional emotion regulation capacities.

# 5 General Discussion

## 5.1 Integration of findings

The present dissertation aimed to identify different pathways of enhancing core processes of social cognition such as emotion recognition and mentalizing as well as emotion regulation.

In study 1, we used a pharmacological approach and aimed at characterizing beneficial effects of intranasal OXT application on the ability to correctly identify avoidance-related emotional expressions. In addition, we were particularly interested whether the effects of OXT on recognizing emotional faces are altered by ELS experience. Our results demonstrate that OXT improved the ability to recognize avoidance-related emotional faces as compared to approach-related emotional faces. Most importantly, whereas the performance for avoidance-related emotions in participants with more ELS experience was comparable in both OXT and placebo condition, OXT particularly enhanced emotion recognition in participants with less ELS experience.

Our results replicate previous studies showing that emotional information from faces is recognized better following OXT application (for a review see Van Ijzendoorn and Bakermans-Kranenburg 2012). Interestingly, this effect was only observed for avoidance-related emotions. This finding is compatible with previous studies, reporting that OXT increases socially oriented or approach-related behaviors and attachment (for a review see Heinrichs et al. 2009). Hence, the effect of OXT seems to be more beneficial for emotional faces that require approach for successful identification, namely avoidance-related emotions. Apparently, the effect of OXT on emotion recognition depends on motivational processes to approach or avoid the presented stimuli (Kemp and Guastella 2011).

Regarding the result that especially participants with less ELS experience benefited most from OXT administration, our data is in line with previous studies indicating that oxytonergic effects on prosocial behaviour are lowered or absent in individuals with adverse experiences during childhood (Meinlschmidt and Heim 2007; Riem et al. 2013; Van Ijzendoorn et al. 2011). This interpretation is supported by an interesting train of evidence regarding the epigenetic regulation of the gene coding for the OXT receptor (OXTR, for a review see Kumsta et al. 2013). It has been suggested that single nucleotide polymorphisms (SNPs) in OXTR are associated with structural and functional

modulations in the limbic circuitry. These regions involve the hippocampus, cingulate gyrus and amygdala that play an important role in social cognition. Consequently, social cognition and behavior can be modulated by variations in OXTR (Meyer-Lindenberg and Tost 2012). It has also been shown that epigenetic states of genes can be affected by environmental factors, specifically by those that happen in sensitive periods early in development. ELS experience such as emotional neglect or physical abuse are therefore likely to affect the development of the central nervous OXT system by altering OXTR methylation (Bakermans-Kranenburg and van Ijzendoorn 2013; Francis et al. 2000; Winslow et al. 2003). This may in turn lead to decreased sensitivity for OXT administration. Kumsta et al. (2013) suggests that the impact of ELS experience on individual socio-emotional functioning is mediated by alterations of central OXT signaling. Additional findings from our own group strengthen this argument about individual differences in reactivity to OXT as a function of ELS experience. For example, Fan et al. (2014) showed that ELS experience decreases resting state functional connectivity between between the right amygdala and the pregenual anterior cingulate cortex. This indicates that the observed changes in functional connectivity may underlie the altered sensitivity to OXT application following ELS experience.
Another study from our group demonstrates that the OXT induced effects in participants with a history of ELS could be even detrimental as compared with participants without early life stress experience (Grimm et al. 2014). Consequently, OXT administration in such participants should be considered carefully. Consistent with this idea, OXT has been shown to actually hinder trust and cooperation in participants with Borderline Personality Disorder (BPD, Bartz et al. 2011a). Given the fact that high levels of ELS experience have been reported in individuals with BPD, ELS might moderate this detrimental effect.

To summarize, whether OXT promotes or hinders prosocial behaviour and social cognition seems to depend on the individuals and their social experiences. In other words, OXT may facilitate prosocial behavior and social cognition but an adverse personal history may reduce these potentially beneficial effects.

In study 2, we investigated a more complex social cognitive process, namely the ability to infer mental states of others. We showed that a single dose of intranasally administered OXT enhances mentalizing abilities. This effect was only observed for

difficult items. Regarding the question whether the effect of OXT on mentalizing is moderated by individual differences in empathy, we demonstrated that only participants with lower empathy scores benefited from OXT application. Given our results from study 1, it is important to note that we controlled for ELS experience in our analysis.

Our findings replicate previous studies about OXT as an enhancer of mentalizing abilities (Domes et al. 2007b; Luminet et al. 2011). However, only those participants who are less attuned to social information (i.e. who are less empathic) benefited from OXT. An interpretation of this effect might be that OXT facilitates the perceptual salience processing of social cues. This enhancement of salience for social cues might in turn lead to increased selective attention to these cues. Supporting this notion, recent studies showed that OXT increases gaze to the eye region, thus accentuating cues that are highly relevant for interpersonal communication (Andari et al. 2010; Guastella et al. 2008a). Consistent results were found in a recent animal study that reports an OXT-induced increase in attention to the eye region in rhesus monkeys (Dal Monte et al. 2014).
Consequently, it might be more helpful for less empathic participants to increase awareness of socially relevant information in the environment to correctly identify mental states of others. On the other hand, OXT had no impact in participants with already high levels of empathy. This explanation is consistent with previous studies that highlight the importance of considering individual differences to better predict the reactivity to OXT application (for a review see Bartz et al. 2011b).
To summarize, the results from study 1 and study 2 suggest that OXT application can be effectively used to facilitate the recognition of basic emotional expressions as well as more complex mental states of others. In addition, the results highlight the importance of considering environmental factors and socio-emotional skills when examining oxytocinergic effects on social cognition. These findings lead to possible implications for future studies which will be discussed later in this chapter.

There are some limitations that need to be acknowledged. The facial stimuli used in study 1 and study 2 were not animated. To increase ecological validity, future studies should develop experimental tasks including more interpersonal situation and real-life contexts. Another limitation lies in the fact that we only included male participants in both studies. Previous studies have reported gender differences in OXT dependent

effects (Domes et al. 2010; Lischke et al. 2012b) indicating that our results might not be generalizable to women.

In study 3, we used tDCS to investigate the effects of increased dlPFC excitability on cognitive reappraisal as indexed by subjective emotional arousal ratings and SCR. While previous studies have demonstrated the efficacy of tDCS in modulating cognitive-affective processes (Boggio et al. 2009; Peña-Gómez et al. 2011), this is the first study to show the potential use of tDCS as a tool to modulate cognitive reappraisal. We demonstrated that anodal tDCS over the right dlPFC during downregulation resulted in lower arousal ratings and decreased SCR. The opposite pattern was observed for the upregulation condition in which anodal tDCS resulted in higher arousal ratings accompanied by marginally enhanced SCR. A considerable strength of this study is the inclusion of gaze fixation analysis to control for attentional deployment during the task. No differences in gaze fixation patterns between the anodal and sham stimulation group were observed. Therefore, it can be concluded that the observed differences in arousal ratings and SCR between the groups do not reflect changes in attentional deployment but rather underly modulations of cognitive reappraisal processes. Our data indicates that tDCS facilitates cognitive reappraisal in both directions by either increasing or decreasing emotional responsiveness depending on the regulatory goal. By showing a relationship between prefrontal tDCS and reappraisal success, our results specifically confirm and expand the role of the dlPFC (Eippert et al. 2007; Ochsner et al. 2004) as an important part of the emotion regulation circuit. This may open up new possibilities for the use of tDCS as an add-on treatment in patients showing dysfunctional emotion regulation capacities.

In the last years, tDCS has emerged as a promising therapeutic intervention in the treatment of affective disorders. However, clinical trials have reported mixed results concerning the efficacy of tDCS with regard to response and remission rates. A meta-analysis on the clinical use of tDCS in the treatment of depression proposes that active tDCS is more effective than sham tDCS in the reduction of depressive symptoms (Kalu et al. 2012). However, recent meta-analyses by Berlim et al. (2013) and Shiozawa et al. (2014) conclude that the clinical utility of tDCS as a treatment for MD still remains unclear. The authors suggest that further studies are needed which include larger samples, investigate long-term effects of tDCS and specify optimal stimulation parameters.

However, there are certain limitations regarding the stimulation protocol that are important to consider. First, our design would have benefited from an additional active stimulation site. With the present study design we cannot answer the question if stimulation of any other brain region besides the dlPFC would have resulted in similar effects. Future studies should identify the effects of tDCS in targeting other brain regions related to cognitive reappraisal. Second, we also cannot rule out the possibility that increasing the excitability of the dlPFC activity may also have modulated the response of other nearby located brain regions. Given the complexity of the emotion regulation network, further brain imaging studies are needed to explore the role of tDCS in modulating cognitive reappraisal.

Third, one may argue that cathodal stimulation of the right supraorbital area might be responsible for the observed effects. For example, neuroimaging studies investigating cognitive reappraisal have identified a network that also includes the orbitofrontal cortex (Ochsner and Gross 2005). We did not directly control for that possible confound by including a control condition (e.g. anodal stimulation over the occipital cortex and cathodal stimulation over the supraorbital cortex). However, we addressed this problem by using a large cathode electrode (10 X 10 $cm^{2)}$. Using a very large electrode should result in functionally unipolar tDCS, which has been demonstrated to be by Nitsche et al. (2007). Given the limitations of the study, our findings need to be replicated and complimented by further studies.

Taken together, the results from all three studies demonstrate the effectiveness of both tDCS and pharmacological challenge using OXT application in enhancing core social cognitive processes. Furthermore, the results from study 1 and study 2 indicate that OXT seems to play a more nuanced role in social cognition and strongly depends on baseline socio-cognitive skills such as empathy as well as environmental factors such as history of ELS.

Although OXT has been successfully used in targeting social cognition in healthy subjects and clinical samples, there is still an ongoing debate about the underlying processes of oxytocinergic effects. However, recent reviews (Guastella and MacLeod 2012; Modi and Young 2012) on the current research about OXT effects on social processing propose the following mechanisms:

1. OXT enhances early allocation of selective attention towards socially-relevant stimuli.
2. OXT increases cognitive appraisal of affect from socially-relevant information.
3. OXT facilitates memory processes for socially-relevant information.
4. OXT magnifies the degree to which socially-relevant information is appraised in a positive manner.
5. OXT links the encoding of socially-relevant stimuli to social reward and reinforcement

Our results from study 1 and study 2 support the view that OXT increases cognitive appraisal from socially-relevant information. That is, participants showed better performance in recognizing basic emotions and more complex emotional states from facial expressions. In study 1, the duration of the face stimuli presentation during the task was set to 200 ms. As reflected in higher accuracy rates for avoidance-related emotions in the OXT group, the pharmacological challenge seems to facilitate early allocation of selective attention. However, this remains an interpretation since we did not use additional methods such as eye tracking or pupillometry to directly assess changes in attention. Although we also did not directly test memory processes in study 1 and study 2, previous results from the same study sample show that OXT improves memory performance for negative social stimuli (Weigand et al. 2013). Interestingly, this effect was more pronounced when participants had been instructed to increase their negative emotions during encoding using cognitive reappraisal strategies. Our data also provides evidence for another possible mechanism that is disregarded in the above-mentioned reviews, namely the role of OXT in enhancing approach-related behaviors and attachment.

The findings from study 2 indicate that especially participants who are less socially proficient (i.e. who are less empathic) benefit from OXT. This points to possible implications for OXT in the treatment of the mental disorders, which are characterized by derogations in core social cognitive domains (as described in chapter 1.1.1, 1.1.2 and 1.1.3). Indeed, evidence for OXT as a means to enhance social cognitive processes has received heightened attention in the last years. Recently, animal models investigating the OXT system have been used to understand the biological mechanisms of mental disorders, which are associated with impaired social cognition. They suggest that

modulation of the OXT system might be a powerful strategy for pharmacological treatments of these social cognitive impairments (Modi and Young 2012). Specifically, it has been shown in animals that OXT ameliorates social cognitive processes such as social information processing and recognition (Ferguson et al. 2001; Jin et al. 2007).

In humans, previous studies have highlighted the effectiveness for OXT in the treatment of autism spectrum disorder (ASD), which is characterized by severe socio-cognitive impairments (Lombardo et al. 2011). First evidence suggests that OXT exerts beneficial effects on various social cognitive domains in ASD on a behavioral (Anagnostou et al. 2012; Andari et al. 2010; Guastella et al. 2010) and neural level (Domes et al. 2013a). Given the evidence that ASD is associated with avoidance of eye contact (Kliemann et al. 2010), the beneficial use of OXT in enhancing gaze shift to the eye region (Gamer et al. 2010) seems promising. In addition to these findings, OXT application has been found to reduce hyperactivity in social anxiety disorder (Labuschagne et al. 2011) and improve certain components of social cognition in schizophrenia (Gibson et al. 2014). A recent review by Modi and Young (2012) underlines the potential of OXT as an add-on-treatment for behavioral therapies. The authors propose, that OXT could facilitate the acquisition of social skills such as mentalizing and emotion recognition as taught in a behavioral therapy program.
The above-mentioned studies support the potential role for OXT in improving key social cognitive processes that are impaired in various mental disorders. Although recent findings are encouraging, the results need to be treated with caution. Human long-term administration studies are needed to clarify long-term effects of OXT treatment, to better understand which specific domains of social cognition can be targeted, and to come up with clinical recommendations (Preti et al. 2014).

Further work could also help to elucidate which brain circuits are modulated by OXT challenge. There is a growing body of research investigating specific brain regions that are affected by OXT application. For example, recent studies indicate that modulation of amygdala activity by OXT might be responsible for the alterations in attentional processes (Gamer et al. 2010; Meyer-Lindenberg et al. 2011; Striepens et al. 2012). However, much less is known about more complex neural networks underlying core social cognitive processed that are modulated by OXT. Only a few studies have investigated OXT-induced changes in functional connectivity (Fan et al. 2014; Sripada et

al. 2013). For example, an interesting study by Gamer et al. (2010) found that enhanced gaze shift to the eye region after OXT application is mediated by increased functional coupling of the posterior amygdala with the superior colliculus. Furthermore, OXT has been found to enhance resting-state connectivity between the amygdala and the medial frontal cortex (Sripada et al. 2013).

Most of the research on OXT effects on social cognition has been conducted without considering individual differences in OXT sensitivity (Guastella and MacLeod 2012). This is surely necessary to first of all prove the ability of OXT to enhance the processing of socially relevant information. However, individual differences are suggested to alter the reactivity to OXT application. Thus, the present findings highlight the necessity of considering socio-emotional competencies and individual biographical factors when investigating the effects of OXT on social cognitive processes. This would be in line with the general idea of personalized medicine in psychiatric treatment, which is proposed to improve individualized diagnostic and therapeutic strategies as a means to enhance treatment efficacy and safety (Zajkowska et al. 2014). Additionally, personalized medicine might allow for a better individual prediction of the treatment outcome.

As indicated by Churchland and Winkielman (2012) "both biological and psychological factors can easily turn a relatively broad physiological effect into what may deceivingly appear to be a narrow behavioral effect" (page 397). This observation gains empirical evidence from the results of study 1 and study 2. That is, we were able to show that OXT has no additional effect for participants with higher baseline socio-emotional abilities as well as for participants with higher levels of ELS experience. Future OXT studies on social cognition in healthy subjects should therefore include additional measures to identify both participants with lower and higher baseline socio-emotional skills as well as participants with and without a history of ELS. This approach might help to avoid false negative results.

Furthermore, previous studies also suggest that OXT application can even have a derogatory effect in participants with a history of ELS (Grimm et al. 2014) and in patients with BPD (Bartz et al. 2011a). Consequently, the author suggest that OXT administration in such participants should be considered carefully to guarantee treatment safety. Given the growing interest for OXT studies in the treatment of mental disorders, future studies should control for ELS experience in clinical samples to avoid detrimental effects following OXT application.

To summarize, the previously mentioned findings support the importance to identify variables that account for personal variability in response to OXT application. Future research is therefore needed to identify key markers that might result in improved predictions about which participants benefit most from OXT application. These key markers should involve variables such as the here investigated baseline socio-emotional abilities (Bartz et al. 2011b) and environmental factors (Bakermans-Kranenburg and Van Ijzendoorn 2013). Further studies are needed to investigate other variables such as genetic factors (Kumsta et al. 2013), gender (Domes et al. 2010), relationship status (Scheele et al 2012), contextual factors (De Dreu et al. 2010) and psychiatric condition (Bartz et al. 2010). Furthermore, application factors such as dosage should be incorporated into the model (Goldman et al. 2011). Given the substantial evidence about the effects of OXT on social cognition, endeavor to link basic and clinical research in the field of neuropeptides and social behavior is promising. This approach might enable researchers to better understand variation in OXT sensitivity, thus facilitating the development of individual therapeutic strategies.

## 5.2 Perspectives

In study 1 and study 2, we investigated OXT effects on core social cognitive processes such as facial emotion recognition and mentalizing. In the next step, we aimed to further explore a possible explanatory mechanism for the observed OXT effects on these processes on a neural level, namely the modulation of selective attention (Andari et al. 2010; Guastella et al. 2008a; Schulze et al. 2011). Given our results from study 1, we were interested in potential modulatory effects of ELS experience on OXT effects.

With regard to the model of cognitive control of emotions by Ochsner et al. (2012), selective attention enables attention to be allocated to specific foci by suppressing the processing of task-irrelevant information. Individual differences in selective attention can be investigated with the emotional interference control task (Etkin et al. 2006). In this task, emotional interference results from incompatibility between the task-relevant and task-irrelevant information of the stimulus (see Figure 13).

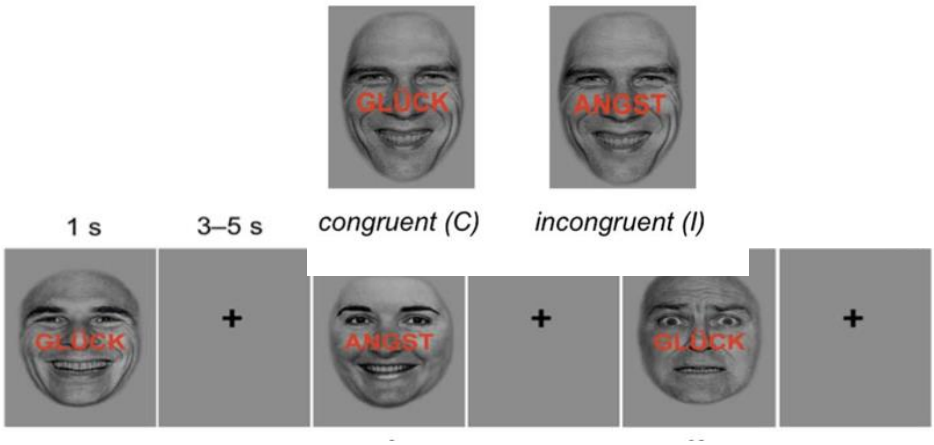


**Fig. 13** Emotional interference task. Basic stimulus material consisting of congruent and incongruent facial expressions/word pairs from eight subjects of the Ekman faces collection (fearful and happy facial expressions; words 'happy' and 'fear'). Each 38 randomized stimuli were presented in six blocks with jittered interstimulus interval.

Accuracy and reaction times for the detection of facial expressions are recorded for each trial. In this task, participants need to specifically shift their attention to relevant features of the face in order to control the interference caused by the automatised word reading. One might hypothesize that OXT decreases emotional interference by directing attention to relevant features of the face (for example the eye region).
Using this task, it has consistently been demonstrated that incongruent vs. congruent trials are associated with longer reaction times and lower accuracy rates (Chechko et al. 2009; Etkin et al. 2006). Additionally, a number of studies in recent years have investigated the underlying neuronal circuit of interference control. Specifically, it has been shown that the anterior cingulate cortex (ACC), the dlPFC and the ventral medial prefrontal cortex (vmPFC) are engaged while participants attempt to control emotional interference (Egner et al. 2008; Etkin et al. 2006; Haas et al. 2006; Iordan et al. 2013). Increased activation in these regions has been observed for inconguent vs. congruent trials. The amygdala seems to reflect the amount of interference with elevated activation in inconguent vs. congruent trials. (Egner et al. 2008; Etkin et al. 2006; Han et al. 2013).

Our study had two main objectives. First, we hypothesized that OXT application would result in an improved recognition rate and faster reaction times for incongruent > congruent trials as compared to the placebo condition. Second, we predicted functional differences between the two experimental conditions in the interference control

network. Specifically, we expected enhanced activation in the ACC and dlPFC and attenuated activation in the amygdala following OXT application.

27 male subjects, aged between 21 and 36 years (mean age= 28.7 SD= 4.3) participated in this double-blind, within-subjects, placebo-controlled trial. All subjects were recruited out of a preexisting psychologically and somatically healthy community-dwelling sample and were screened for psychiatric disorders. They received either OXT (Syntocinon Spray; Novartis, Basel, Switzerland) or a placebo intranasally in two separate experimental sessions. Functional data were acquired on a Siemens Trio 3T scanner using a standard echo planar imaging sequence.

Our preliminary analysis revealed the following results: Independent of OXT application, we observed the expected pattern of longer reaction times and decreased accuracy rate for incongruent vs. congruent trials. However, no effect for OXT application on accuracy and reaction times was found. In addition, ROI analysis revealed no differences in activation for OXT application vs placebo in the previously defined regions.

Interestingly, we observed differences in the interference control network as a function of ELS experience. That is, independent of OXT application, participants with a history of ELS experience showed stronger recruitment of the amygdala in the incongruent fear > congruent fear condition. Furhermore, increased ACC activation for incongruent happy > congruent happy trials was found. In the next step, functional connectivity analyses need to be conducted as well as a possible interaction between OXT application and ELS experience needs to be investigated.

# 6 References

Adams RB Jr, Kleck RE (2005) Effects of direct and averted gaze on the perception of facially communicated emotion. Emotion 5(1):3-11.

Adophs R (2002) Neural systems for recognizing emotion. Current Opinion in Neurobiology 12:169-177.

Adolphs R (2009) The Social Brain: Neural Basis of Social Knowledge. Annu Rev Psychol 60:693–716.

Adolphs R (2010) What does the amygdala contribute to social cognition? Ann N Y Acad Sci 1191:42-61.

Adolphs R, Baron-Cohen S, Tranel D (2002) Impaired Recognition of Social Emotions following Amygdala Damage. J Cogn Neurosci 14(8):1264-1274.

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, Ed 4. American Psychiatric Press, Washington, DC.

Anagnostou E, Soorya L, Chaplin W, Bartz J, Halpern D, Wasserman S, Wang AT, Pepa L, Tanel N, Kushki A, Hollander E (2012) Intranasal oxytocin versus placebo in the treatment of adults with autism spectrum disorders: a randomized controlled trial. Mol Autism 3(1):16.

Andari E, Duhamel JR, Zalla T, Herbrecht E, Leboyer M, Sirigu A (2010) Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. Proceedings of the National Academy of Sciences of the United States of America 107(9):4389-4394.

Anderson AK, Phelps EA (2001) Lesions of the human amygdala impair enhanced perception of emotionally salient events. Nature 411(6835):305-309.

Andrews SC, Hoy KE, Enticott, PG, Daskalakis ZJ, Fitzgerald PB (2011) Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain stimulation 4:84-89.

Andrews-Hanna JR, Saxe R, Yarkoni T (2014) Contributions of episodic retrieval and mentalizing to autobiographical thought: Evidence from functional neuroimaging, resting-state connectivity, and fMRI meta-analyses. Neuroimage 91:324-335.

Aron AR, Robbins TW, Poldrack RA (2004) Inhibition and the right inferior frontal cortex. Trends in Cognitive Science 8:170-177.

Averbeck BB, Bobin T, Evans S, Shergill SS (2012) Emotion recognition and oxytocin in patients with schizophrenia. Psychological Medicine 42(2):259-266.

Baeken C, De Raedt R, Van Schuerbeek P, Vanderhasselt MA, De Mey J, Bossuyt A, Luypaert R (2010) Right prefrontal HF-rTMS attenuates right amygdala processing of

negatively valenced emotional stimuli in healthy females. Behavioural Brain Research 214:450–455.

Bakermans-Kranenburg MJ, van Ijzendoorn MH (2013) Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. Translational Psychiatry 3:e258.

Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Phan KL (2007) Amygdala-frontal connectivity during emotion regulation. Soc Cogn Affect Neurosci 4:303-312.

Baron-Cohen S (1995) Mindblindness: An essay on autism and theory of mind. MIT Press, Cambridge, MA.

Baron-Cohen S, Tager-Flusberg H, Cohen JD (Eds.) (2000) Understanding Other Minds: Perspectives from Developmental Cognitive Neuroscience, second ed. Oxford University Press, New York.

Baron-Cohen S, Wheelwright S (2004) "The Empathy Quotient: An Investigation Of Adults With Asperger Syndrome Or High Functioning Autism, And Normal Sex Differences". Journal of Autism and Developmental Disorders 34 (2):163–175.

Baron-Cohen S, Wheelwright S, Hill J (2001) The 'Reading the mind in the eyes' test revised version: a study with normal adults, and adults with asperger syndrome or high-functioning autism. Journal of Child Psychology and Psychiatry 42:241–252.

Bartz JA, Hollander E (2006) The neuroscience of affiliation: Forging links between basic and clinical research on neuropeptides and social behavior. Hormones and Behavior 50: 518-528.

Bartz J, Simeon D, Hamilton H, Kim S, Crystal S, Braun A, Vicens V, Hollander E (2011a) Oxytocin can hinder trust and cooperation in borderline personality disorder. Soc Cogn Affect Neurosci 6(5):556-563.

Bartz JA, Zaki J, Bolger N, Hollander E, Ludwig NN, Kolevzon A, Ochsner KN (2010) Oxytocin selectively improves empathic accuracy. Psychological Science 21(10):1426-1428.

Bartz JA, Zaki J, Bolger N, Ochsner KN (2011b) Social effects of oxytocin in humans: context and person matter. Trends in Cognitive Sciences 15:301–309.

Bassili JN (1979) Emotion recognition: The role of facial movement and the relative importance of upper and lower areas of the face. Journal of Personality and Social Psychology 37(11):2049-2058.

Baumgartner T, Heinrichs M, Vonlanthen A, Fischbacher U, Fehr E (2008) Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron 58:639–650.

Beauregard M, Paquette V, Lévesque J (2006) Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. Neuroreport 17(8):843-846.

Beer JS, Ochsner KN (2006) Social cognition: A multi level analysis. Brain Research 1079:98–105.

Benedek M, Kaernbach CA (2010) Continuous measure of phasic electrodermal activity. Journal of Neuroscience Methods 190:80-91.

Berking M, Wupperman P (2012) Emotion regulation and mental health: recent findings, current challenges, and future directions. Curr Opin Psychiatry 25(2):128-134.

Berlim MT, Van den Eynde F, Daskalakis ZJ (2013) Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. J Psychiatr Res 47(1):1-7.

Bermond B, Bierman DJ, Cladder MA, Moormann PP, Vorst HC (2010) The cognitive and affective alexithymia dimensions in the regulation of sympathetic responses. International Journal of Psychophysiology 75(3):227-233.

Bernstein DP, Fink L (1998) Childhood Trauma Questionnaire: A retrospective self-report manual. The Psychological Corporation, San Antonio, TX.

Besel LDS, Yuille JC (2010) Individual differences in empathy: The role of facial expression recognition. Personality and Individual Differences 49(2):107–112.

Bielsky IF, Young LJ (2004) Oxytocin, vasopressin, and social recognition in mammals. Peptides 25(9): 1565-1574.

Blair RJR (2003) Facial expressions, their communicatory functions and neurocognitive substrates. Philosophical Transactions of The Royal Society: B Biological Sciences 358:561–572.

Blair KS, Geraci M, Smith BW, Hollon N, DeVido J, Otero M, Blair JR, Pine DS (2012) Reduced dorsal anterior cingulate cortical activity during emotional regulation and top-down attentional control in generalized social phobia, generalized anxiety disorder, and comorbid generalized social phobia/generalized anxiety disorder. Biol Psychiatry 72(6):476-482.

Boggio PS, Zaghi S, Fregni F (2009) Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia 47:212-217.

Brockmeyer T, Bents H, Holtforth MG, Pfeiffer N, Herzog W, Friederich HC (2012) Specific emotion regulation impairments in major depression and anorexia nervosa. Neuroimage 61(3):686-693.

Bromberg-Martin ES, Matsumoto M, Hikosaka O (2010) Dopamine in motivational control: Rewarding, aversive, and alerting. Neuron 68: 815–834.

Brunoni AR, Vanderhasselt MA, Boggio PS, Fregni F, Dantas EM, Mill JG, Lotufo PA, Bensenor IM (2013) Polarity- and valence-dependent effects of prefrontal transcranial

direct current stimulation on heart rate variability and salivary cortisol. Psychoneuroendocrinology 38(1):58-66.

Calder A J, Burton AM, Miller P, Young AW, Akamatsu S (2001) A principal component analysis of facial expressions. Vision Research 41:1179-1208.

Campbell A (2010) Oxytocin and human social behavior. Personality and Social Psychology Review 14(3): 281-295.

Carter CS, Grippo AJ, Pournajafi-Nazarloo H, Ruscio MG, Porges SW (2008) Oxytocin, vasopressin and sociality. Progress in Brain Research 170:331-336.

Cattaneo Z, Devlin JT, Salvini F, Vecchi T, Silvanto J (2010a) The causal role of category-specific neuronal representations in the left ventral premotor cortex (PMv) in semantic processing. Neuroimage 49:2728–2734.

Cattaneo L, Sandrini M, Schwarzbach J (2010b) State-Dependent TMS Reveals a Hierarchical Representation of Observed Acts in the Temporal, Parietal, and Premotor Cortices. Cerebral Cortex 20:2252-2258.

Cavanna AE, Trimble MR (2006) The precuneus: A review of its functional anatomy and behavioural correlates. Brain 129(3):564-583.

Chechko N, Wehrle R, Erhardt A, Holsboer F, Czisch M, Sämann PG (2009) Unstable prefrontal response to emotional conflict and activation of lower limbic structures and brainstem in remitted panic disorder.PloS One 4(5):e5537.

Churchland PS, Winkielman P (2012) Modulating social behavior with oxytocin: how does it work? What does it mean? Horm Behav 61:392–399.

Corona G, Jannini EA, Vignozzi L, Rastrelli G, Maggi M (2012) The hormonal control of ejaculation. Nat. Rev. Urol. 9:508–519.

Cosmides L, Tooby J (2004) Social exchange: The evolutionary design of a neurocognitive system, In: Gazzaniga, M.S. (Ed.), The Cognitive Neurosciences, 3rd ed. MIT Press, Cambridge, MA.

Costa PTM (1992) Revised NEO Personality inventory and NEO five-factor inventory (Professional Manual). Psychological Assessment Resources, Odessa.

Craig JS, Hatton C, Craig FB, Bentall RP (2004) Persecutory beliefs, attributions and theory of mind: comparison of patients with paranoid delusions, Asperger's syndrome and healthy controls. Schizophrenia Research 69:29–33.

Critchley HD (2009) Psychophysiology of neural, cognitive and affective integration: fMRI and autonomic indicants. International Journal of Psychophysiology 73:88-94.

Curtis CE, D'Esposito M (2003) Persistent activity in the prefrontal cortex during working memory. Trends in Cognitive Science 7:415–423.

Dal Monte O, Noble PL, Costa VD, Averbeck BB (2014) Oxytocin enhances attention to the eye region in rhesus monkeys. Frontiers in Neuroscience 8:41.

Damasio AR, Damasio H (1994) Cortical systems for retrieval of concrete knowledge: The convergence zone framework. In C. Koch (Ed.), Large-scale neuronal theories of the brain. MIT Press, Cambridge, MA.

Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, Domschke K, Hohoff C, Ohrmann P, Bauer J, Lindner C, Postert C, Konrad C, Arolt V, Heindel W, Suslow T, Kugel H (2012) Limbic Scars: Long-Term Consequences Of Childhood Maltreatment Revealed by Functional and Structural Magnetic Resonance Imaging. Biological Psychiatry 71(4):286-293.

Davidson RJ (1992) Anterior cerebral asymmetry and the nature of emotion. Brain and Cognition 20:125–151.

Davidson RJ, Abercrombie H, Nitschke JB, Putnam K (1999) Regional brain function, emotion and disorders of emotion. Current Opinion in Neurobiology 9:228–234.

Davidson RJ, Irwin W, Anderle MJ, Kalin NH (2003a) The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry 160:64 –75.

Davidson RJ, Scherer KR, Goldsmith HH (2003b) Handbook of affective sciences. Oxford University Press, New York.

Dawson ME, Schell AM, Filion DL (2000) The electrodermal system. In: Cacioppo JT, Tassinary LG, Bernston GL, editors. Handbook of Psychophysiology. Cambridge University Press, Cambridge.

De Dreu CKW, Greer LL, Handgraaf MJJ, Shalvi S, Van Kleef GA, Baas M, Ten Velden FS, Van Dijk E, Feith SW (2010) The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans. Science 328:1408–1411.

Di Simplicio M, Massey-Chase R, Cowen PJ, Harmer CJ (2009) Oxytocin enhances processing of positive versus negative emotional information in healthy male volunteers. Journal of Psychopharmacology 23:241–248.

Dockery CA, Hueckel-Wenig R, Birbaumer N, Plewnia C (2009) Enhancement of planning ability by transcranial direct current stimulation. The Journal of Neuroscience 29:7271–7277.

Domes G, Heinrichs M, Gläscher J, Büchel C, Braus DF, Herpertz SC (2007a) Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biological Psychiatry 62:1187-1190.

Domes G, Heinrichs M, Kumbier E, Grossmann A, Hauenstein K, Herpertz SC (2013a) Effects of intranasal oxytocin on the neural basis of face processing in autism spectrum disorder. Biol Psychiatry 74(3):164-171.

Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC (2007b) Oxytocin improves "mind-reading" in humans. Biological Psychiatry 61(6):731–733.

Domes G, Lischke A, Berger C, Grossmann A, Hauenstein K, Heinrichs M, Herpertz SC (2010) Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology 35:83-93.

Domes G, Sibol M, Schulze L, Lischke A, Herpert SC, Heinrichs M (2013b) Intranasal oxytocin increases covert attention to positive social cues. Psychological Medicine 43(8):1747-1753.

Donaldson ZR, Young LJ (2008) Oxytocin, vasopressin, and the neurogenetics of sociality. Science 322 (5903):900-904.

Driscoll D, Tranel D, Anderson SW (2009) The effects of voluntary regulation of positive and negative emotion on psychophysiological responsiveness. Int J Psychophysiol 72(1):61-66.

Egner T, Etkin A, Gale S, Hirsch J (2008) Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. Cereb Cortex 18(6):1475-1484.

Eippert F, Veit R, Weiskopf N, Erb M, Birbaumer N, Anders S (2007) Regulation of emotional responses elicited by threat-related stimuli. Human brain mapping 28:409-423.

Ekman P, Friesen WV (1971) Constants across cultures in the face and emotion. Journal of Personality and Social Psychology 17(2):124-129.

Elliot AJ, Covington MV (2001) Approach and avoidance motivation. Educational Psychology Review 13(2): 73-92.

Erk S, Mikschl A, Stier S, Ciaramidaro A, Gapp V, Weber B, Walter H (2010) Acute and Sustained Effects of Cognitive Emotion Regulation in Major Depression. The Journal of Neuroscience 30(47):15726-15734.

Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J (2006) Resolving Emotional Conflict: A Role for the Rostral Anterior Cingulate Cortex in Modulating Activity in the Amygdala. Neuron 51:871–882.

Evans SL, Dal Monte O, Noble P, Averbeck BB (2013) Intranasal oxytocin effects on social cognition: A critique. Brain Res [Epub ahead of print].

Fan Y, Herrera-Melendez AL, Pestke K, Feeser M, Aust S, Otte C, Pruessner JC, Böker H, Bajbouj M, Grimm S (2014) Early life stress modulates amygdala-prefrontal functional connectivity: Implications for oxytocin effects. Human Brain Mapping 35(10):5328-5339.

Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A (2007) Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. The Journal of Neuroscience 27:12500–12505.

Fehlinger T, Stumpenhorst M, Stenzel N, Rief W (2013) Emotion regulation is the essential skill for improving depressive symptoms. J Affect Disord 144(1-2):116-122.

Feldman R, Weller A, Zagoory-Sharon O, Levine A (2007) Evidence for a neuroendocrinological foundation of human affiliation – plasma oxytocin levels across pregnancy and the postpartum period predict mother–infant bonding. Psychological Science 18:965–970.

Ferguson JN, Aldag JM, Insel TR, Young LJ (2001) Oxytocin in the medial amygdala is essential for social recognition in the mouse. J Neurosci 21(20):8278-8285.

Fett AK, Viechtbauer W, Dominguez MD, Penn DL, van Os J, Krabbendam L (2011) The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci Biobehav Rev 35:573–588.

Fischer-Shofty M, Shamay-Tsoory SG, Harari H, Levkovitz Y (2010) The effect of intranasal administration of oxytocin on fear recognition. Neuropsychologia 48:179–184.

Fonagy P, Gergely G, Target M (2007) The parent-infant dyad and the construction of the subjective self. Journal of Child Psychology and Psychiatry 48:288–328.

Francis DD, Champagne FC, Meaney MJ (2000) Variations in maternal behaviour are associated with differences in oxytocin receptor levels in the rat. Journal of Neuroendocrinology 12(12):1145-1148.

Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MT, Paulus W, Pascual-Leone A (2005) Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 166:23-30.

Fries AB, Ziegler TE, Kurian JR, Jacoris S, Pollak SD (2005) Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior. Proceedings of the National Academy of Sciences of the United States of America 102:17237–17240.

Frijda N (1986) The emotions. Cambridge University Press, Cambridge.

Frith U (2001) Mind blindness and the brain in autism. Neuron 32:969–979.

Frith CD (2008) Social cognition. Philos Trans R Soc Lond B Biol Sci 363:2033–2039.

Frith CD, Frith U (2006a) The neural basis of mentalizing. Neuron 50:531-534.

Frith CD, Frith U (2006b) How we predict what other people are going to do. Brain Research 1079:36–46.

Frith CD, Frith U (2012) Mechanisms of social cognition. Annu Rev Psychol 63:287-313.

Fulford D, Peckham AD, Johnson K, Johnson SL (2014) Emotion perception and quality of life in bipolar disorder. J Affect Disord 152–154:491–497.

Gallagher HL, Frith CD (2003) Functional imaging of `theory of mind´. Trends in Cognitive Sciences 7(2):77-83.

Gamer M, Büchel C (2012) Oxytocin specifically enhances valence-dependent parasympathetic responses. Psychoneuroendocrinology 37(1):87-93.

Gamer M, Zurowski B, Büchel C (2010) Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. Proceedings of the National Academy of Sciences of the United States of America 107(20):9400-9405.

Gibson CM, Penn DL, Smedley KL, Leserman J, Elliott T, Pedersen CA (2014) A pilot six-week randomized controlled trial of oxytocin on social cognition and social skills in schizophrenia. Schizophr Res 156(2-3):261-265.

Gimpl G, Fahrenholz F (2001) The oxytocin receptor system: structure, function, and regulation. Physiological Reviews 81(2):629–683.

Glenn CR, Klonsky ED (2009) Emotion dysregulation as a core feature of borderline personality disorder. J Pers Disord 23(1):20-28.

Goeleven E, Raedt RD, Leyman L, Verschuere B (2008) The Karolinska Directed Emotional Faces: A validation study. Cognition and Emotion 22:1094-1118.

Goldin PR, Gross JJ (2010) Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. Emotion 10(1):83-91.

Goldman MB, Gomes AM, Carter CS, Lee R (2011) Divergent effects of two different doses of intranasal oxytocin on facial affect discrimination in schizophrenic patients with and without polydipsia. Psychopharmacology (Berl) 216(1):101-110.

Grant MM, Cannistraci C, Hollon SD, Gore J, Shelton R (2011) Childhood trauma history differentiates amygdala response to sad faces within MDD. Journal of Psychiatric Research 45(7): 886–895.

Grimm S, Pestke K, Feeser M, Aust S, Weigand A, Wang J, Wingenfeld K, Pruessner JC, La Marca R, Böker H, Bajbouj M (2014) Early life stress modulates oxytocin effects on limbic system during acute psychosocial stress. Social Cognitive and Affective Neuroscience 9(11):1828-1835.

Groppe SE, Gossen A, Rademacher L, Hahn A, Westphal L, Gründer G, Spreckelmeyer KN (2013) Oxytocin influences processing of socially relevant cues in the ventral tegmental area of the human Brain. Biological Psychiatry 74(3):172-179.

Gross JJ. (2002) Emotion regulation: Affective, cognitive, and social consequences. Psychophysiology 39:281-291.

Gross JJ, John OP (2003) Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. Journal of Personality and Social Psychology 85:348-362.

Gross JJ, Muñoz RF (2006) Emotion Regulation and Mental Health. American Psychological Association, Clinical Psychology: Science and Practice 2(2):151- 164.

Gross JJ, Thompson RA (2007) Emotion regulation. Conceptual foundations. In: Gross JJ, editor. Handbook of emotion regulation. Guilford Publications, New York.

Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ, Hicki IB (2010) Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. Biological Psychiatry 67:692–694.

Guastella AJ, MacLeod C (2012) A critical review of the influence of oxytocin nasal spray on social cognition in humans: evidence and future directions. Horm Behav 61(3):410-418.

Guastella AJ, Mitchell PB, Dadds MR (2008a) Oxytocin Increases Gaze to the Eye Region of Human Faces. Biological Psychiatry 63(1):3-5.

Guastella AJ, Mitchell PB, Mathews F (2008b) Oxytocin enhances the encoding of positive social memories in humans. Biological Psychiatry 64(3): 256-258.

Haas BW, Omura K, Constable RT, Canli T (2006) Interference produced by emotional conflict associated with anterior cingulate activation. Cogn Affect Behav Neurosci 6(2):152-156.

Han HJ, Lee K, Kim HT, Kim H (2014) Distinctive amygdala subregions involved in emotion-modulated Stroop interference. Soc Cogn Affect Neurosci 9(5):689-698.

Harmon-Jones E, Gable PA, Peterson CK (2010) The role of asymmetric frontal cortical activity in emotion-related phenomena: a review and update. Biological Psychology 84(3):451-462.

Harms MB, Martin A, Wallace GL (2010) Facial emotion recognition in autism spectrum disorders: a review of behavioral and neuroimaging studies. Neuropsychol Rev 20(3):290-322.

Hartley CA, Phelps EA (2010) Changing Fear: The Neurocircuitry of Emotion Regulation. Neuropsychopharmacology 35(1):136-146.

Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB (2009) Lower CSF oxytocin concentrations in women with a history of childhood abuse. Molecular Psychiatry 14:954–958.

Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U (2003) Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biological Psychiatry 54:1389–1398.

Heinrichs M, von Dawans B, Domes G (2009) Oxytocin, vasopressin, and human social behavior. Frontiers in Neuroendocrinology 30(4): 548-557.

Heller AS, Johnstone T, Light SN, Peterson MJ, Kolden GG, Kalin NH, Davidson RJ (2013) Relationships Between Changes in Sustained Fronto-Striatal Connectivity and Positive Affect in Major Depression Resulting From Antidepressant Treatment. Am J Psychiatry 170(2):197-206.

Hoertnagl CM, Hofer A (2014) Social cognition in serious mental illness. Curr Opin Psychiatry 27(3):197-202.

Hooker CI, Verosky SC, Germine LT, Knight RT, D'Esposito M (2008) Mentalizing about emotion and its relationship to empathy. Social Cognitive and Affective Neuroscience 3:204-217.

Hooker CI, Verosky SC, Germine LT, Knight RT, D'Esposito M (2013) Neural activity during social signal perception correlates with self-reported empathy. Brain Research 1308:100-113.

Huber E (1931) Evolution of facial musculature and facial expression. Johns Hopkins Press, Oxford, England.

Humphrey NK (1976) The social function of intellect. In: Bateson PPG, Hinde RA, editors. Growing points in ethology. Cambridge University Press, Cambridge, England.

Hurlemann R, Patin A, Onur OA, Cohen MX, Baumgartner T, Metzler S, Dziobek I, Gallinat J, Wagner M, Maier W, Kendrick KM (2010) Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. The Journal of Neuroscience 30(14): 4999-5007.

Hysek CM, Domes G, Liechti ME (2012) MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions. Psychopharmacology (Berl). 222(2):293-302.

Iordan AD, Dolcos S, Dolcos F (2013) Neural signatures of the response to emotional distraction: a review of evidence from brain imaging investigations. Front Hum Neurosci 7:200.

Irwin, JR, McClelland GH (2003) Negative Consequences of Dichotomizing Continuous Predictor Variables. Journal of Marketing Research, 40(3):366–371.

Jin D, Liu HX, Hirai H, Torashima T, Nagai T, Lopatina O, Shnayder NA, Yamada K, Noda M, Seike T, Fujita K, Takasawa S, Yokoyama S, Koizumi K, Shiraishi Y, Tanaka S, Hashii M, Yoshihara T, Higashida K, Islam MS, Yamada N, Hayashi K, Noguchi N, Kato I, Okamoto H, Matsushima A, Salmina A, Munesue T, Shimizu N, Mochida S, Asano M, Higashida H (2007) CD38 is critical for social behaviour by regulating oxytocin secretion. Nature 446(7131):41-45.

Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ (2007) Failure to Regulate: Counterproductive Recruitment of Top- Down Prefrontal-Subcortical Circuitry in Major Depression. J Neurosci 27(33):8877-8884.

Judd CM, McClelland GH, Ryan CR (2009) Data analysis: A model comparison approach (2nd ed.). Routledge.

Kadosh RC, Muggleton N, Silvanto J, Walsh V (2010) Double Dissociation of Format-Dependent and Number-Specific Neurons in Human Parietal Cortex. Cerebral Cortex 20:2166-2171.

Kalu UG, Sexton CE, Loo CK, Ebmeier KP (2012) Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med 42(9):1791-1800.

Kana RK, Libero LE, Hu CP, Deshpande HD, Colburn JS (2014) Functional brain networks and white matter underlying theory-of-mind in autism. Soc Cogn Affect Neurosci 9(1):98-105.

Kanske P, Heissler J, Schönfelder S, Bongers A, Wessa M (2011) How to regulate emotions? Neural networks for reappraisal and distraction. Cerebral Cortex 21:1379-1388.

Kanske P, Heissler J, Schönfelder S, Wessa M (2012) Neural correlates of emotion regulation deficits in remitted depression: the influence of regulation strategy, habitual regulation use, and emotional valence. Neuroimage 61(3):686-693.

Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, Brunelin J, Möller HJ, Reiser M, Padberg F (2011) Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J Neurosci 31(43):15284-15293.

Kemp AH, Guastella AJ (2010) Oxytocin: prosocial behavior, social salience, or approach-related behavior? Biol. Psychiatry 67:e33–e34 author reply e35.

Kemp AH, Guastella AJ (2011) The role of Oxytocin in human affect: A novel hypothesis. Current Directions in Psychological Science 20:222-231.

Keverne EB, Kendrick KM (1992) Oxytocin facilitation of maternal behavior in sheep. Annals of the New York Academy of Science 652:83-101.

Kim SH, Hamann S (2012) The effect of cognitive reappraisal on physiological reactivity and emotional memory. International Journal of Psychophysiology 83:348-356.

Kincses TZ, Antal A, Nitsche MA, Bartfai O, Paulus W (2004) Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. Neuropsychologia 42:113–117.

Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, Gruppe H, Mattay VS, Gallhofer B, Meyer-Lindenberg A (2005) Oxytocin modulates neural circuitry for social cognition and fear in humans. The Journal of Neuroscience 25(49): 11489-11493.

Kliemann D, Dziobek I, Hatri A, Steimke R, Heekeren HR (2010) Atypical reflexive gaze patterns on emotional faces in autism spectrum disorders. J Neurosci 30(37):12281-12287.

Klin A, Jones W, Schultz R, Volkmar F, Cohen D (2002) Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. Arch Gen Psychiatry 59:809–816.

Koenigs M, Ukueberuwa D, Campion P, Grafman J, Wassermann E (2009) Bilateral frontal transcranial direct current stimulation: Failure to replicate classical findings in healthy subjects. Clinical Neurophysiology 120:80-84.

Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E (2005) Oxytocin increases trust in humans. Nature 435:673–676.

Kumsta R, Hummel E, Chen FS, Heinrichs M (2013) Epigenetic regulation of the oxytocin receptor gene: implications for behavioral neuroscience. Front Neurosci 7:83.

Labuschagne I, Phan KL, Wood A, Angstadt M, Chua P, Heinrichs M, Stout JC, Nathan PJ (2011) Medial frontal hyperactivity to sad faces in generalized social anxiety disorder and modulation by oxytocin. Int J Neuropsychopharmacol 14:1-14.

Lang P (1995) The emotion probe: Studies of motivation and attention. American Psychologist 52:372–385.

Lang PJ, Bradley MM, Cuthbert BN (2001) International Affective Picture System (IAPS): Instruction manual and affective ratings. Technical report A-5. University of Florida, Gainesville, FL.

Lehrl S, Triebig G, Fischer B (1995) Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta Neurologica Scandinavica 91:335–345.

Leist T, Dadds MR (2009) Adolescents' ability to read different emotional faces relates to their history of maltreatment and type of psychopathology. Clinical Child Psychology and Psychiatry 14(2):237-250.

Leknes S, Wessberg J, Ellingsen DM, Chelnokova O, Olausson H, Laeng B (2013) Oxytocin enhances pupil dilation and sensitivity to 'hidden' emotional expressions. Social Cognitive and Affective Neuroscience 8(7):741-749.

Leppänen JM, Milders M, Bell JS, Terriere E, Hietanen JK (2004) Depression biases the recognition of emotionally neutral faces. Psychiatry Res 128(2):123-133.

Leslie AM, Friedman O, German TP (2004) Core mechanisms in "theory of mind". Trends in Cognitive Science 8(12):528–533.

Leyman L, De Raedt R, Vanderhasselt MA, Baeken C (2008) Influence of high-frequency repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex on the inhibition of emotional information in healthy volunteers. Psychol Med 39:1019–1028.

Lieberman MD (2007a) Social cognitive neuroscience: a review of core processes. Annu Rev Psychol 58:259-289.

Lieberman MD (2007b) Putting feelings into words: affect labeling disrupts amygdala activity in response to affective stimuli. Psychological Science 18:421-428.

Lippold OC, Redfearn JW (1964) Mental changes resulting from the passage of small direct currents through the human brain. Br J Psychiatry 110:768-772.

Lischke A, Berger C, Prehn K, Heinrichs M, Herpertz SC, Domes G (2012a) Intranasal oxytocin enhances emotion recognition from dynamic facial expressions and leaves eye-gaze unaffected. Psychoneuroendocrinology 37:475–481.

Lischke A, Gamer M, Berger C, Grossmann A, Hauenstein K, Heinrichs M, Herpertz SC, Domes G (2012b) Oxytocin increases amygdala reactivity to threatening scenes in females. Psychoneuroendocrinology 37:1431-1438.

Lombardo MV, Chakrabarti B, Bullmore ET, MRC AIMS Consortium, Baron-Cohen S (2011) Specialization of right temporo-parietal junction for mentalizing and its relation to social impairments in autism. Neuroimage 56(3):1832-1838.

Loup F, Tribollet E, Dubois-Dauphin M, Dreifuss JJ (1991) Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. Brain Research 555:220–232.

Luminet O, Grynberg D, Ruzette N, Mikolajczak M (2011) Personality- dependent effects of oxytocin: greater social benefits for high alexithymia scorers. Biological Psychology 87:401–406.

Lundqvist D, Flykt A, Öhman A (1998) The Karolinska Directed Emotional Faces - KDEF, CD ROM from Department of Clinical Neuroscience, Psychology section, Karolinska Institutet, ISBN 91-630-7164-9.

MacDonald E, Dadds MR, Brennan JL, Williams K, Levy F, Cauchi AJ (2011) A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research. Psychoneuroendocrinology 36:1114–1126.

Maeoka H, Matsuo A, Hiyamizu M, Morioka S, Ando H (2012) Influence of transcranial direct current stimulation of the dorsolateral prefrontal cortex on pain related emotions: a study using electroencephalographic power spectrum analysis. Neuroscience Letters 512(1):12-16.

Maheu FS, Dozier M, Guyer AE, Mandell D, Peloso E, Poeth K, Jenness J, Lau JY, Ackerman JP, Pine DS, Ernst M (2010) A preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. Cognitive, Affective, & Behavioral Neuroscience 10(1):34-49.

Mangina CA, Beuzeron-Mangina JH (1996) Direct electrical stimulation of specific humain brain structures and bilateral electrodermal activity. International Journal of Psychophysiology 22:1-8.

Mantella RC, Vollmer RR, Li X, Amico JA (2003) Female oxytocin-deficient mice display enhanced anxiety-related behavior. Endocrinology 144:2291–2296.

Masten CL, Guyer AE, Hodgdon HB, McClure EB, Charney DS, Ernst M, Kaufman J, Pine DS, Monk CS (2008) Recognition of facial emotions among maltreated children with high rates of post-traumatic stress disorder. Child Abuse & Neglect 32:139-153.

Marsh AA, Yu HH, Pine DS, Blair RJ (2010) Oxytocin improves specific recognition of positive facial expressions. Psychopharmacology 209:225–232.

Martin RA, Berry GE, Dobranski T van Home M (1996) Emotion perception threshold: individual differences in emotional sensitivity. Journal of Research in Personality 38:290-305.

Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT (1997) Cingulate function in depression: a potential predictor of treatment response. Neuroreport 8:1057–1061.

Meinlschmidt G, Heim C (2007) Sensitivity to intranasal Oxytocin in adult men with early parental separation. Biological Psychiatry 61(9):1109-1111.

Melis MR, Melis T, Cocco C, Succu S, Sanna F, Pillolla G, Boi A, Ferri GL, Argiolas A (2007) Oxytocin injected into the ventral tegmental area induces penile erection and increases extracellular dopamine in the nucleus accumbens and paraventricular nucleus of the hypothalamus of male rats. European Journal of Neuroscience 26:1026–1035.

Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M (2011) Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nature Reviews Neuroscience 12(9):524-538.

Meyer-Lindenberg A, Tost H (2012) Neural mechanisms of social risk for psychiatric disorders. Nat Neurosci 15(5):663-668.

Mikolajczak M, Pinon N, Lane A, de Timary P, Luminet O (2010) Oxytocin not only increases trust when money is at stake, but also when confidential information is in the balance. Biological Psychology 85:182–184.

Miranda PC, Lomarev M, Hallett M (2006) Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol 117:1623–1629.

Mischel W, Shoda Y (1995) A Cognitive-Affective System Theory of Personality: Reconceptualizing Situations, Dispositions, Dynamics, and Invariance in Personality Structure. Psychological Review 102(2):246-268.

Modi ME, Young LJ (2012) The oxytocin system in drug discovery for autism: animal models and novel therapeutic strategies. Horm Behav 61(3):340-350.

Moor BG, Macks ZA, Gürog˘lu B, Rombouts SA, Molen MW, Crone EA (2012) Neurodevelopmental changes of reading the mind in the eyes. Social Cognitive and Affective Neuroscience 7:44–52.

Mothersill O, Morris DW, Kelly S, Rose EJ, Bokde A, Reilly R, Gill M, Corvin AP, Donohoe G (2014) Altered medial prefrontal activity during dynamic face processing in schizophrenia spectrum patients. Schizophr Res [Epub ahead of print].

Nitsche MA, Doemkes S, Karaköse T, Antal A, Liebetanz D, Lang N, Tergau F, Paulus W (2007) Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol 97:3109-3117.

Nitsche MA, Koschack J, Pohlers H, Hullemann S, Paulus W, Happe S (2012) Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans. Frontiers in Psychiatry 3:58.

Nitsche MA, Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol 527:633–639.

Ochsner KN (2004) Current directions in social cognitive neuroscience. Curr Opin Neurobiol 14(2):254-258.

Ochsner KN, Gross JJ (2005) The cognitive control of emotion. Trends in Cognitive Sciences 9:242-249.

Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, Gross JJ (2004) For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage 23:483-499.

Ochsner KN, Silvers, JA, Buhle JT (2012) Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Annals of the New York Academy of Sciences 1251:E1-24.

Olff M, Frijling JL, Kubzansky LD, Bradley B, Ellenbogen MA, Cardoso C, Bartz JA, Yee JR, van Zuiden M (2013) The role of oxytocin in social bonding, stress regulation and mental health: An update on the moderating effects of context and interindividual differences. Psychoneuroendocrinology 38:1883-1894.

Parker JDD, Graeme JT, Bagby RM (2003) The 20-item Toronto Alexithymia Scale III. Reliability and factorial validity in a community population. Journal of Psychosomatic Research 55:269-275.

Pelphrey KA, Sasson NJ, Reznick JS, Paul G, Goldman BD, Piven J (2002) Visual scanning of faces in autism. J Autism Dev Disord 32:249–261.

Peña-Gómez C, Vidal-Piñeiro D, Clemente IC, Pascual-Leone Á, Bartrés-Faz D (2011) Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. PLoS One 6(7):e22812.

Pereira JB, Junqué C, Bartrés-Faz D, Martí MJ, Sala-Llonch R, Compta Y, Falcón C, Vendrell P, Pascual-Leone A, Valls-Solé J, Tolosa E (2013) Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson´s disease. Brain Stimulation 6(1):16-24.

Petrovic P, Kalisch R, Singer T, Dolan RJ (2008) Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. The Journal of Neuroscience 28:6607-6615.

Phillips ML, Drevets WC, Rauch SL, Lane R (2003) Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biol Psychiatry 54:515–528.

Plazier M, Joos K, Vanneste S, Ost J, De Ridder D (2012) Bifrontal and bioccipital transcranial direct current stimulation (tDCS) does not induce mood changes in healthy volunteers: a placebo controlled study. Brain Stimulation 5(4):454-461.

Pollak SD, Kistler DJ (2002) Early experience is associated with the development of categorical representations for facial expressions of emotion. Proceedings of the National Academy of Sciences of the United States of America 99(13):9072-9076.

Pollak SD, Messner M, Kistler DJ, Cohn JF (2009) Development of perceptual expertise in emotion recognition. Cognition 110:242–247.

Prehn K, Kazzer P, Lischke A, Heinrichs M, Herpertz SC, Domes G (2013) Effects of intranasal oxytocin on pupil dilation indicate increased salience of socioaffective stimuli. Psychophysiology 50(6):528-537.

Preti A, Melis M, Siddi S, Vellante M, Doneddu G, Fadda R (2014) Oxytocin and autism: a systematic review of randomized controlled trials. J Child Adolesc Psychopharmacol 24(2):54-68.

Price JL (2005) Free will versus survival: brain systems that underlie intrinsic constraints on behavior. J Comp Neurol 493:132–139.

Quirin M, Kuhl J, Dusing R (2011) Oxytocin buffers cortisol responses to stress in individuals with impaired emotion regulation abilities. Psychoneuroendocrinology 36:898–904.

Riem MM, Bakermans-Kranenburg MJ, Huffmeijer R, van Ijzendoorn MH (2013) Does intranasal oxytocin promote prosocial behavior to an excluded fellow player? A randomized-controlled trial with Cyberball. Psychoneuroendocrinology 38(8):1418-1425.

Ring RH, Malberg JE, Potestio L, Ping J, Boikess S, Luo B, Schechter LE, Rizzo S, Rahman Z, Rosenzweig-Lipson S (2006) Anxiolytic-like activity of oxytocin in male mice: behavioral and autonomic evidence, therapeutic implications. Psychopharmacology (Berl) 185: 218–225.

Rive MM, van Rooijen G, Veltman DJ, Phillips ML, Schene AH, Ruhé HG (2013) Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. Neurosci Biobehav Rev 37:2529-2553.

Rosa MA, Lisanby SH (2012) Somatic treatments for mood disorders. Neuropsychopharmacology 37:102-116.

Ross HE, Young LJ (2009) Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. Frontiers in Neuroendocrinology 30:534-547.

Rutherford HJV, Lindell AK (2011) Thriving and surviving: Approach and avoidance motivation and lateralization. Emotion Review 3(3):333-343.

Savaskan E, Ehrhardt R, Schulz A, Walter M, Schachinger H (2008) Post-learning intranasal oxytocin modulates human memory for facial identity. Psychoneuroendocrinology 33(3):368-374.

Saxe R, Carey S, Kanwisher N (2004) Understanding other minds: linking developmental psychology and functional neuroimaging. Annual Review of Psychology 55:87–124.

Saxe R, Wexler A (2005) Making sense of another mind: The role of the right temporo-patietal junction. Neuropsychologia 43:1391–1399.

Scheele D, Striepens N, Güntürkün O, Deutschländer S, Maier W, Kendrick KM, Hurlemann R (2012) Oxytocin Modulates Social Distance between Males and Females. The Journal of Neuroscience 32(46): 16074-16079.

Scher CD, Murray BS, Asmundson GJG, McCreary DR, Forde DR (2001) The Childhood Trauma Questionnaire in a Community Sample: Psychometric Properties and Normative Data. Journal of Traumatic Stress 14(4):843-857.

Schulze L, Lischke A, Greif J, Herpertz SC, Heinrichs M, Domes G (2011) Oxytocin increases recognition of masked emotional faces. Psychoneuroendocrinology 36:1378–1382.

Schuppert HM, Giesen-Bloo J, van Gemert TG (2009) Effectiveness of an emotion regulation group training for adolescents- a randomized controlled pilot study. Clin Psychol Psychother 16(6):467-478.

Senju A, Southgate V, White S, Frith U (2009) Mindblind eyes: an absence of spontaneous theory of mind in Asperger syndrome. Science 325(5942):883-885.

Shahrestani S, Kemp AH, Guastella AJ (2013) The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis. Neuropsychopharmacology 38(10): 1929-1936.

Shahrokh DK, Zhang TY, Diorio J, Gratton A, Meaney MJ (2010) Oxytocin-dopamine interactions mediate variations in maternal behavior in the rat. Endocrinology 151:2276–2286.

Shiozawa P, Fregni F, Benseñor IM, Lotufo PA, Berlim MT, Daskalakis JZ, Cordeiro Q, Brunoni AR (2014) Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. Int J Neuropsychopharmacol 1-10. [Epub ahead of print].

Silvanto J, Muggleton N, Walsh V (2008) State-dependency in brain stimulation studies of perception and cognition. Trends in Cognitive Sciences 12(12):447-454.

Singer T (2006) The neuronal basis and ontogeny of empathy and mind reading: review of literature and implications for future research. Neuroscience and Biobehavioral Reviews 30(6):855-863.

Sripada CS, Phan KL, Labuschagne I, Welsh R, Nathan PJ, Wood AG (2013) Oxytocin enhances resting-state connectivity between amygdala and medial frontal cortex. Int J Neuropsychopharmacol 16(2):255-260.

Steyer R, Schwenkmezger P, Notz P, Eid M (1997) Der Mehrdimensionale Befindlichkeitsfragebogen (MDBF). Hogrefe-Verlage für Psychologie, Göttingen, Bern, Toronto, Seattle.

Striepens N, Scheele D, Kendrick KM, Becker B, Schäfer L, Schwalba K, Reul J, Maier W, Hurlemann R (2012) Oxytocin facilitates protective responses to aversive social stimuli in males. Proceedings of the National Academy of Sciences of the United States of America 109:18144–18149.

Svaldi J, Griepenstroh J, Tuschen-Caffier B, Ehring T (2012) Emotion regulation deficits in eating disorders: a marker of eating pathology or general psychopathology? Psychiatry Res 197(1-2):103-111.

Thompson RA (1994) Emotion regulation: a theme in search of definition. In: Fox NA, editor. Monographs of the society for research in child development, 59, p. 25-52.

Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin JD, Casey BJ (2011) Elevated amygdala response to faces following early deprivation. Developmental Science 14(2):190-204.

Urry HL, van Reekum CM, Johnstone T (2006) Amygdala and Ventromedial Prefrontal Cortex Are Inversely Coupled during Regulation of Negative Affect and Predict the Diurnal Pattern of Cortisol Secretion among Older Adults. The Journal of Neuroscience 26(16):4415– 4425.

Urry HL, van Reekum CM, Johnstone T, Davidson RJ (2009) Individual diferences in some (but not all) medial prefrontal regions reflect cognitive demand while regulating unpleasant emotion. Neuroimage 47:852-863.

van Reekum CM, Johnstone T, Urry HL, Thurow ME, Schaefer HS, Alexander AL (2007) Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect. NeuroImage 36:1041-1055.

Van Ijzendoorn MH, Bakermans-Kranenburg MJ (2012) A sniff of trust: Meta-analysis of the effects of intranasal oxytocin administration on face recognition, trust to in-group, and trust to out-group. Psychoneuroendocrinology 37:438-443.

Van Ijzendoorn MH, Huffmeijer R, Alink LR, Bakermans-Kranenburg MJ, Tops M (2011) The impact of Oxytocin administration on charitable donating is moderated by experiences of parental love-withdrawal. Frontiers in Psychology 2:258.

Venta A, Hart J, Sharp C (2013) The relation between experiental avoidance, alexithymia and emotion regulation in inpatient adolescents. Clinical Child Psychology and Psychiatry;18(3):398-410.

Vuilleumier P, Armony JL, Driver J, Dolan RJ (2003) Distinct spatial frequency sensitivities for processing faces and emotional expressions. Nature Neuroscience 6: 624– 631.

Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN (2008) Prefrontal-subcortical pathways mediating successful emotion regulation. Neuron 59(6):1037-1050.

Wager TD, Jonides J, Reading S (2004) Neuroimaging studies of shifting attention: a meta-analysis. Neuroimage 22:1679-1693.

Weber MJ, Messing SB, Rao H, Detre JA, Thompson-Schill SL (2014) Prefrontal transcranial direct current stimulation alters activation and connectivity in cortical and subcortical reward systems: A tDCS-fMRI study. Hum Brain Mapp [Epub ahead of print].

Weigand A, Feeser M, Gärtner M, Brandt E, Fan Y, Fuge P, Böker H, Bajbouj M, Grimm S (2013) Effects of intranasal oxytocin prior to encoding and retrieval on recognition memory. Psychopharmacology 227(2):321-329.

Winslow JT, Noble PL, Lyons CK, Sterk SM, Insel TR (2003) Rearing effects on cerebrospinal fluid oxytocin concentration and social buffering in rhesus monkeys. Neuropsychopharmacology 28(5):910-918.

Wittchen HU, Wunderlich U, Gruschwitz S, Zaudig M (1997) SKID-I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Hogrefe, Göttingen.

Wolkenstein L, Plewnia C (2013) Amelioration of cognitive control in depression by transcranial direct current stimulation. Biological Psychiatry 73(7):646-651.

Woud ML, Holmes EA, Postma P, Dalgleish T, Mackintosh B (2012) Ameliorating intrusive memories of distressing experiences using computerized reappraisal training. Emotion 12(4):778-784.

Zajkowska ZE, Englund A, Zunszain PA (2014) Towards a personalized treatment in depression: endocannabinoids, inflammation and stress response. Pharmacogenomics 15(5):687-698.

## 7 Eidesstattliche Erklärung

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

Berlin, den 08.07.2014

_____

Melanie Feeser

# 8 Curriculum Vitae

For reasons of data protection,
the curriculum vitae is not included in the online version

# 9 List of Publications

## 9.1 First author publications

**Feeser M**, Fan Y, Weigand A, Hahn A, Gärtner M, Aust S, Böker H, Bajbouj M, Grimm S (2014) The beneficial effect of Oxytocin on avoidance- related facial emotion recognition depends on early life stress experience. Psychopharmacology (Berl.) 231(24):4735-4744.

**Feeser M**, Fan Y, Weigand A, Hahn A, Gärtner M, Böker H, Grimm S, Bajbouj M (2015) Oxytocin improves mentalizing – Pronounced effects for individuals with attenuated ability to empathize. Psychoneuroendocrinology (in minor revision).

**Feeser M**, Prehn K, Kazzer P, Mungee A, Bajbouj M (2014) Transcranial direct current stimulation enhances cognitive control during emotion regulation. Brain Stimulation 7(1):105-112.

**Feeser M**, Schlagenhauf F, Sterzer P, Park S, Stoy M, Gutwinski S, Kienast T, Bauer M, Heinz A, Ströhle A, Bermpohl F (2013) Context insensitivity during positive and negative emotional expectancy in depression. Psychiatry Research 212(1):28-35.

## 9.2 Co-author publications

Fan Y, Herrera-Melendez AL, Pestke K, **Feeser M**, Aust S, Otte C, Pruessner JC, Böker H, Bajbouj M, Grimm S (2014) Early life stress modulates amygdala-prefrontal functional connectivity: implications for oxytocin effects. Human Brain Mapping 35(10):5328-5339.

Fan Y, Pestke K, **Feeser M**, Aust S, Pruessner JC, Böker H, Bajbouj M, Grimm S (2015) Amygdala-hippocampal connectivity changes during acute psychosocial stress: Joint effect of early life stress and oxytocin. Neuropsychopharmacology [in revision].

Fuge P, Aust S, Fan Y, Weigand A, Gärtner M, **Feeser M,** Bajbouj M, Grimm S (2014) Interaction of Early Life Stress and Corticotropin-Releasing Hormone Receptor Gene: Effects on working memory. Biological Psychiatry 76(11):888-894.

Fuge P, Grimm S, Weigand A, Fan Y, Gärtner M, **Feeser M**, Bajbouj M (2014) Assessment of age- Related Changes in Cognitive Functions Using EmoCogMeter, a novel tablet-computer based approach. Journal of Visualized Experiments (84):e50942.

Grimm S, Gärtner M, Fuge P, Fan Y, Weigand A, **Feeser M**, Aust S, Heekeren HR, Jacobs A, Heuser I, Bajbouj M (2015) Variation in the corticotropin-releasing hormone receptor 1 (CRHR1) gene modulates age effects on working memory. Journal of Psychiatric Research 61:57-63.

Grimm S, Pestke K, **Feeser M**, Aust S, Weigand A, Wang J, Wingenfeld W, Pruessner JC, La Marca R, Böker H, Bajbouj M (2014) Early life stress modulates oxytocin effects on limbic system during acute psychosocial stress. Social Cognitive and Affective Neuroscience 9(11):1828-1835.

Mungee A, Kazzer P, **Feeser M**, Nitsche M, Schiller D, Bajbouj M (2014) Transcranial direct current stimulation of the prefrontal cortex: a means to modulate fear memories. Neuroreport 25(7):480-484.

Weigand A, **Feeser M**, Gärtner M, Brandt E, Fan Y, Fuge P, Böker H, Bajbouj M, Grimm S (2013) Effects of intranasal oxytocin prior to encoding and retrieval on recognition memory. Psychopharmacology (Berl). 227(2):321-329.

Weigand A, Richtermeier A, **Feeser M**, Guo JS, Briesemeister B, Grimm S, Bajbouj M (2013) State-dependent effects of prefrontal repetitive transcranial magnetic stimulation on emotional working memory. Brain Stimulation 6(6):905-912

## 10 Conference Poster Presentations

**Feeser M** et al. (2010) Transcranial direct current stimulation of the prefrontal cortex modulates attention and physiological arousal during emotion regulation. DGPPN-Kongress, Berlin.

**Feeser M** et al. (2011) Age related differences in emotion regulation and its impact on episodic memory processes. DGPPN-Kongress, Berlin.

**Feeser M** et al. (2011) Transcranial direct current stimulation of the prefrontal cortex modulates physiological arousal during emotion regulation. SOBP, San Francisco.

**Feeser M** et al. (2012) Effects of intranasal oxytocin on implicit emotion regulation and associated brain activity. HBM, Bejing.

## 11 Conference Talks

**Feeser M** et al. (2011) Modulation der Rekonsolidierung emotionaler Gedächtnisinhalte durch tDCS. Jahrestagung der dt. Gesellschaft für Hirnstimulation, Halle.

**Feeser M** et al. (2012) Effects of intranasal oxytocin on implicit emotion regulation and associated brain activity. DGPPN-Kongress, Berlin.