Touching upon affiliation:

On the roles of the opioid and oxytocin systems in human social-emotional behavior

Isabell Marie Meier

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On the roles of the opioid and oxytocin systems in human social-emotional behavior

Raken aan verbondenheid:
over de rol van opioïde en oxytocine systemen in menselijk sociaal-emotioneel gedrag

(met een samenvatting in het Nederlands)

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(mit einer Zusammenfassung in deutscher Sprache)

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To my family

Table of contents

Chapter 1 **9**
General Introduction

Chapter 2 **19**
A mu-Opioid Feedback Model of Human Social Behavior

Chapter 3 **37**
Naltrexone increases negatively-valenced facial responses to happy faces in female participants

Chapter 4 **47**
Oxytocin increases reactivity in the amygdala and hippocampus to emotional stimuli of children in women depending on childhood emotional neglect

Chapter 5 **69**
Social touch increases dominant gaze in social confrontations

Chapter 6 **81**
General Discussion

References **89**

Author Contributions **107**

Nederlandse Samenvatting **111**

Deutsche Zusammenfassung **117**

Acknowledgements **123**

Curriculum Vitae and personal statement **129**

Publications **133**

Chapter 1

General Introduction

"Nature has placed mankind under the governance of two sovereign masters, pain and pleasure."
Jeremy Bentham

Humans are fundamentally social animals. Other animals are faster, stronger, have the advantage of better sense of smell or vision than humans do. Since we depend on each other for survival, complex social skills are important and necessary for communication, formation and maintenance of social bonds, conflict resolution and cooperation. These superb abilities bring sensitivities: the experience of being excluded from a group of friends or being rejected from a partner is remarkably painful, up to a physical level with feelings of tightness and pain in the chest. In the long-term, social isolation and perceived loneliness are known risk factors for physical and mental health problems, activating stress related psychological and neurobiological mechanisms (Cacioppo et al., 2015). The aversiveness of the experience of social rejection, which has been shown to activate neural networks related to pain processing (Eisenberger, 2012), is argued to motivate the individual to find social comfort and possibly adapt their behavior to a more successful strategy for social bonding. At the same time, the feeling of spending time with close others, receiving a tight hug from a friend or seeing the smile of one's child is rewarding in itself, easily recognizable by a warm feeling and a sense of ease and pleasure. This feeling of pleasure from the social interaction leads to the formation of stronger social bonds that in the long-term may act as a protective buffer from stress (Kikusui et al., 2006). It is therefore not surprising that complex social-emotional behaviors that support affiliation and protect us and others in our social environment, such as the ability to understand others' intentions and feelings, are claimed to be largely based on fundamental mechanisms involved in pain and pleasure. Two underlying neurobiological systems that have been shown to be involved in both pain and reward processing, and are crucial for establishing and maintaining bonds with others, are the oxytocin and opioid systems.

The field of social neuroscience is dedicated to the study of the neural and neurochemical factors that drive social-emotional behavior, combining questions and experimental methods from the field of social psychology with approaches from neuroendocrinology, affective neuroscience, psychopharmacology and behavioral genetics. This thesis aims to systematically investigate aspects of social-emotional behavior that contribute to social affiliation and protect the individual from the aversive consequences of experiences like social rejection and isolation, with a focus on the role of oxytocin and opioid systems there-within. There are basic, automatic-, and more complex, higher order processes that modulate affiliative motivation. In this thesis I will consider the contribution emotional mimicry, the automatic facial response to seeing somebody else's emotion (chapter 3), and gaze behavior as a marker of social motivation (chapter 5), to affiliative behavior. Further, I will investigate two central components of social-emotional communication which are essential for affiliation and social buffering: empathy, the ability to read, understand and share others' emotions (chapter 4), and touch which acts via its pleasurable hedonic quality and its function as a buffer for social pain (chapter 5). Last, and most importantly, throughout the thesis I will discuss the contribution of the opioid and oxytocin systems to the underlying mechanisms of these behaviors and abilities.

Opioid and Oxytocin modulation of social-emotional behavior

Morphine, the active ingredient of opium which itself is an extract from the opium poppy Papaver somniferum, was first isolated by Sertürner in 1804. Historically though, the earliest records on the usage of opium go back to the Sumerians in 3000 BC indicating that it was used for both recreational and ritual practices as well as medicinal ones (Brownstein, 1993). It is the analgesic effects associated specifically with the mu-opioid receptor (MOR) system, through which the highly efficient pain killer morphine exerts its effects, that made the MOR system an interesting target for medical, and subsequently, social research. Mu-opioid receptors are largely distributed throughout the entire brain, with high concentration in areas involved in reward and pain processing including the ventral striatum, periaqueductal gray, substantia nigra, thalamus, amygdala, hippocampus, and cortical areas such as the cingulate- and prefrontal cortex (Pfeiffer et al., 1982; Sprenger et al., 2005). The euphoric properties of opioids, combined with their role in addiction brought more popular attention to the opioids, but also made research of its social properties more complicated due to ethical considerations. Early animal research though, suggests a more diverse role for endogenous opioids, mediating affect, social behavior and attachment (McNally, 2009; Panksepp et al., 1978). More recently, human social neuroscience has started to explore the potential of endogenous opioids by investigating the function of the MOR system, demonstrating that indeed, opioids shape the hedonic components of affect, affective learning processes and memory, and therewith contribute to behaviors and abilities such as empathy that facilitate affiliation (Eippert et al., 2008; Haaker et al., 2017; Loseth et al., 2014; Meier et al., 2016; Nummenmaa et al., 2016; Ribeiro et al., 2005; Syal et al., 2015).

Another system known for its prominent role in affiliation and for its diverse effects on social behavior is the oxytocin system. Oxytocin is a neuromodulatory hormone that is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. From the hypothalamic nuclei, neurons project directly to target regions in the central nervous system (CNS) including the amygdala and the nucleus accumbens (Nacc) for central effects of oxytocin, and further to the posterior pituitary gland from where oxytocin is released into the bloodstream exerting peripheral effects (Bos et al., 2012). Oxytocin is well known for its essential role in parent-infant bonding, being released during parturition and breast-feeding, and for its role in partner preference and bonding. Oxytocin further has analgesic and anxiolytic properties, and regulates a whole range of social behaviors including social perception and learning, cooperation and trust, different components of empathy, and emotion regulation (Bos et al., 2012; De Dreu et al., 2010; Olff et al., 2013; Shamay-Tsoory and Abu-Akel, 2016). An important aspect to consider is that the effects of oxytocin are strongly dependent on context and individual factors. Olff et al. (2013) proposed that the perceived ‘safety’ of a context might modulate the function of oxytocin and the associated expressed behaviors, facilitating either defensive (perceived negative/ unsafe context) or pro-social behaviors that promote bonding (perceived positive/ safe context). On the level of individual characteristics, oxytocin may selectively increase social abilities in

individuals that show deficiencies in the first place, possibly by increasing and orienting attention to relevant social cues (Bartz et al., 2011).

Considering the functional role of both endogenous opioids and oxytocin in affiliation and pain processing, suggests interactive modulation of social behavior by the two systems. Animal research indicates that the antinociceptive effects of oxytocin, and possibly oxytocin's effects on reward processing, are achieved through interaction with the MOR system (Gu and Yu, 2007). At the same time, oxytocin has been shown to inhibit opioid tolerance (Kovacs et al., 1987), which implies that recurrent release of oxytocin might maintain the sensitivity to opioidergic social reward mechanisms (Panksepp et al., 1994). This interactive effect adds explanatory value to why strong social bonds protect from addiction and points toward a possibly important collaborative role of the two systems in relationship maintenance.

Taking a step back and looking at the foundation of complex human social-emotional behavior it becomes apparent that mechanisms of pain and reward processing which we share with other animals, are at the foundation of social behaviors that encompass protective (threat processing and learning, touch) or affiliative functions (reward processing, empathy, touch). The current thesis will therefore target how affective behavioral mechanisms and neurobiological factors contribute to social-emotional behaviors that sustain affiliative and protective motives.

To affiliate and protect

A crucial aspect of bonding and affiliation is that it is rewarding in itself, no external motivators are necessary for us to enjoy social interactions. Importantly, both, the MOR system and oxytocin are mediators of social reward (Bos et al., 2012; Trezza et al., 2011). In humans, neural and behavioral components of social reward can be triggered by simple social interaction cues such as a smile or touch, which invite for approach, attractiveness of the interaction partner or erotic cues (Buchel et al., 2018; Chelnokova et al., 2014; Dunbar, 2010; Meier et al., 2016). Moreover, automatic behaviors to social reward cues, such as the imitation of positive facial expressions, act as a booster of social affiliation (see chapter 3). The primary function attributed to the MOR system within social reward processing is mediating the hedonic value of social interactions, with consequences for reward learning and memory formation (Syal et al., 2015). Indeed, human research showed that MOR activity mediates the hedonic liking of-, and motivation to keep seeing attractive social stimuli, with increased MOR activity through morphine administration (an overview of relevant opioid agonists and antagonists for this thesis can be found in chapter 2) resulting in a bias towards the options that had the highest reward value (Chelnokova et al., 2014). Further, animal studies on social play, an activity that is intrinsically rewarding, crucial for development and bonding, found modulation of play by the MOR system (Trezza et al., 2010; Vanderschuren et al., 1995).

Oxytocin's effects on social reward are possibly mediated through interactions with the opioid- and dopamine system (Bethlehem et al., 2014; Groppe et al., 2013), with oxytocin attributing

salience and orienting attention resources toward socially relevant cues, depending on context and individual characteristics (Bartz et al., 2011; Shamay-Tsoory and Abu-Akel, 2016). This results in the effects of oxytocin being more complex. For example, oxytocin enhanced activation in the ventral tegmental area (VTA), an important structure in the reward circuitry, in response to both cues signaling social reward and punishment (Groppe et al., 2013). Furthermore, oxytocin was found to reduce neural responses to rewarding images of infants in women (Bos et al., 2018). At the same time, oxytocin increased the neural reward response in men, specifically when viewing the face of their female partner (Scheele et al., 2013), suggesting differential effects of oxytocin depending on sex of the participant, or the type of task or reward stimulus used.

At the same time, to safely navigate our social environment, it is crucial to respond in an adaptive manner to cues that predict potential danger. This counts for natural threats, such as the sight of an aggressive dog, as well as learned associations of cues that predict potential danger like the sound of a fire alarm. When we are confronted with a perceived threat, a variety of physiological and behavioral responses are triggered. Heart rate, blood pressure and respiration change, muscle tension increases and the body releases stress hormones. The individual becomes more sensitive to potential signals of danger in their surrounding and reactions to potentially threatening, sudden events are potentiated. On a subjective level the individual feels increased nervousness and arousal. These reactions are part of the human defense system and facilitate fight or flight responses which from an evolutionary perspective secure the individuals survival. The defensive system allows us to respond adequately to threat, and to learn associations to better predict danger and form threat related memories. It is essential however, that, eventually, the reactions to threat stop and the bodily system turns back from a defensive to a more relaxed state. Impairment in the ability to dynamically regulate the response of the defensive system with changing situational factors is associated with affective disorder such as post-traumatic stress disorder (PTSD) and anxiety (Hartley and Phelps, 2010).

Next to their modulation of reward and pain, oxytocin and opioids regulate stress and modulate the processing of threat. Animal and human research suggest an inhibitory role for the endogenous MOR system in threat related processing and learning, by reducing the neural response to threat cues and therewith adjusting the sensitivity and motivation to engage with such (Eippert et al., 2008; Haaker et al., 2017; McNally, 2009; Westbrook et al., 1991). Further, pharmacological activation of the MOR system reduced the subjective experience of stress and the cortisol response associated with the stressful experience (Bershad et al., 2015), in line with the idea of a protective role of the MOR system in acute stress situations. Both rodent and human research support stress-reducing effects of oxytocin on a subjective, physiological and endocrine level (Bos et al., 2012; Heinrichs et al., 2003; Olff et al., 2013). The effects of oxytocin on neural responses to threat have been found to be sex-specific (Domes et al., 2010; Lieberz et al., 2019) and dependent on individual characteristics such as trait levels of anxiety, PTSD or experience of childhood adverse events (Frijling et al., 2016, 2015; Koch et al., 2016; Labuschagne et al., 2010).

A behavioral response to experiencing stress is looking for social support and comfort. Touch simultaneously supports social affiliation and acts as a social support mechanism, decreasing stress and bias to threat (Brummelman et al., 2018; Field, 2010; Jakubiak and Feeney, 2016a). From an affiliative perspective, touch acts as a social support mechanism, communicates emotions and is essential for social bonding (Field, 2010). In a consensual context touch has clear beneficial psychological and physiological effects, it increased trust and a sense of security (Brummelman et al., 2018; Jakubiak and Feeney, 2016b), reduced negative affective facial responses (Mayo et al., 2018), and activated neural responses associated with pleasant affective processing (Bolognini et al., 2013; Lindgren et al., 2012; Lucas et al., 2015). Results concerning the role of oxytocin and opioids in the soothing and stimulating effects of touch, on the other hand, are varied and depend on context, as well as the experimental task, manipulation and measurement output used. Several studies in humans and non-human primates found increased levels of peripheral oxytocin after touch (Ellingsen et al., 2016; Light et al., 2005; Odendaal and Meintjes, 2003; Pederson et al., 1988), however the results of studies investigating the effects of oxytocin administrations on touch are less clear cut. Oxytocin was found to enhance perceived pleasantness and neural responses to touch in one study (Scheele et al., 2014), but no effects of oxytocin on touch pleasantness were found in another study (Ellingsen et al., 2014). Evidence from research investigating the effects of MOR blockade in rhesus macaques suggests the possibility of a distinct role of the opioidergic modulation of touch in mother-infant attachment compared to adult relationships. MOR blockade resulted in instant reduction of grooming in adult relationships but a slow reduction in mother-infant relationships (Martel et al., 1993). Human evidence of opioid modulation of touch is, similar to what is found on oxytocin, rather inconclusive. An increase of pleasantness after MOR blockade was reported in one study, whereas another found no evidence of opioid modulation of touch (Case et al., 2016; Løseth et al., 2019). So far however, human studies seem to have focused on a mechanistic (c-tactile fiber activation) rather than on the social component of touch. Seeing that social touch has regulatory effects on the HPA axis and on the subjective perception of stress in situations of social support (Ditzen et al., 2007), further investigation of the underlying neurobiology of social touch seems promising.

The capacity of touch to convey affection and provide comfort to someone in distress, is indirectly relying on the ability to recognize and understand another person's emotional state. Therefore, empathy, the ability to read, understand and share another person's emotions, is highly relevant for affiliation and attachment from parent-infant-, over partner- and peer relationships, to interactions with unknown others – by increasing communication, interindividual understanding and caregiving behaviors (Decety and Svetlova, 2012). Empathy is a complex phenomenon though that can be divided into two main aspects, the ability to read and understand the emotions and intentions of others (cognitive empathy), and the ability to share another person's affective state (affective empathy) which I will focus on in this thesis. It is argued that affective empathy, which is largely based on structures of the limbic system, has developed in

support of rapid and effective processing of affective states (Decety and Svetlova, 2012). Depending on the valence (positive or negative) of the affective state, approach or avoidance tendencies are triggered which are underlying motivators of affiliative or protective behaviors. A fundamental example to consider when investigating the contribution of neurobiological mechanisms to empathy as an affiliative mechanism is the most fundamental bond in mammalian species, the parent-infant bond. The release of oxytocin during birth and during social interactions of parents with their children facilitates emotion recognition, shared affect and approach, all abilities and behaviors crucial for caregiving and attachment (Bos, 2017; Feldman, 2017; Nelson and Panksepp, 1998). Indeed, parents, compared to non-parents, showed an increased reward response to infant laughter, and a shift from an amygdala-driven aversive-, to a neural emotion regulatory and empathic response to infant crying (Decety and Svetlova, 2012). A similar shift in the neural response to infant crying was found in nulliparous women after oxytocin administration (Riem et al., 2011).

In addition to contributing to the affiliative function of empathy, oxytocin as well as opioid systems, might have a protective role with respect to sharing affect by reducing personal distress when observing somebody else's pain. Empathy for pain, activating behavioral and neural responses that relate to the actual experience of pain (Lamm et al., 2011, 2008; Singer et al., 2004), is accompanied by a varying degree of personal distress which can contribute to a feeling of urgency and helping behavior, but not if it is overpowering. Whether another person's distress activates helping behavior (approach) or an aversive response (avoidance) is therefore dependent on regulation of personal distress. Thus, considering the pain reducing properties of both oxytocin and opioids, it is likely that they also regulate empathy for pain by reducing personal distress toward others' pain, which in turn protects the individual from stress and facilitates helping behavior. Indeed, blocking the MOR system increased negative affect and reduced placebo analgesia toward pain observed in others (Rutgen et al., 2015), and the neural activation related to empathy for pain was reduced after administration of oxytocin, in line with its pain reducing properties (Bos et al., 2015).

However, other studies investigating the effect of oxytocin on empathy for pain found an increase of subjective empathy reports under specific circumstances, emphasizing the complexity of oxytocin effects on social behavior (Abu-Akel et al., 2015; Shamay-Tsoory et al., 2013) as well as the need for further investigation with attention to contextual factors and individual characteristics (see chapter 4).

Outline of this thesis

The thesis is composed of a theoretical overview and three experimental reports. Starting with the review and theoretical perspective on the role of the endogenous MOR in social-emotional behavior, Chapter 2 proposes a 'Mu-opioid feedback model of social behavior'. The model suggests that through its key function of attributing hedonic value to positive and negative so-

cial stimuli, the MOR system regulates affiliative or protective responses to social stimuli, with long-term consequences for social behavior and mental health.

Chapter 3 addresses the question whether blocking the MOR system pharmacologically with naltrexone disrupts the imitation of emotional facial expressions, an automatic behavioral marker of social affiliation (cf. Lakin & Chartrand, 2003; Lakin, Jefferis, Cheng, & Chartrand, 2003; Seibt, Mühlberger, Likowski, & Weyers, 2015). We measured facial responses with electromyography (EMG) in a double-blind, placebo controlled between-subject design. With opioids mediating the subjective pleasantness of social rewards (Chelnokova et al., 2014) as well as the feeling of social connection (Inagaki, 2018, 2016), we propose that the MOR system also regulates the underlying behavioral responses to affective cues and affiliation.

Oxytocin is crucial in caregiving and the perception of social signals in children. Research suggests though, that early adverse experiences can result in long-lasting changes in neural, endocrinological and social functioning (Bos, 2017; Kraaijenvanger et al., 2019), which modulate oxytocin effects. Therefore, in chapter 4, we investigated the effect of oxytocin on the sensitivity to rewarding signals from children and affective empathic responses toward children in situations of distress. We administered oxytocin compared to placebo in a double-blind within-subject design in a functional magnet resonance imaging (fMRI) set up. Additionally, we investigated whether parental caretaking motivation or early adverse experiences modulated the effects oxytocin on social reward and empathy.

The last experimental chapter, chapter 5, describes a study where we researched the effects of social touch on gaze behavior to subliminally presented emotional content. We used infrared eye-tracking to investigate the effects of touch on speed of gaze-aversion from eye-contact, an implicit marker of dominance-submissive behavior. In previous work, we reported slower gaze-aversion from subliminally presented facial anger in subjects with high levels of social dominance and low levels of social anxiety. The beneficial effects of touch as a social buffer, which include stress relief, reduced bias to threat, increased exploration and a higher sense of security (Brummelman et al., 2018; Ditzen et al., 2007; Jakubiak and Feeney, 2016 a&b) might therefore induce the implicit behavioral tendency to engage in social challenges, which is in line with dominant social behavior.

Chapter 2

A mu-Opioid Feedback Model of Human Social Behavior

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Submitted

Abstract

Since the discovery of pain relieving and rewarding properties of opiates such as morphine or heroin, the human mu-opioid system has been a target for medical research on pain processing and addiction. Indeed, pain and pleasure act mutually inhibitory on each other and the mu-opioid system has been suggested as an underlying common neurobiological mechanism. Recently, research interest extended the role of the endogenous mu-opioid system beyond the hedonic value of pain and pleasure towards human social-emotional behavior. Here we propose a mu-opioid feedback model of social behavior. This model is based upon recent findings of opioid modulation of human social learning, bonding and empathy in relation to affiliative and protective tendencies. Fundamental to the model is that the mu-opioid system reinforces socially affiliative or protective behavior in response to positive and negative social experiences with long-term consequences for social behavior and health. The functional implications for stress, anxiety, depression and attachment behaviors are discussed.

Introduction

Pain and pleasure are essential forces of human social-emotional behavior. There is continuous competition between the processing of-, and action preference for pain avoidance and achievement of pleasure. Whilst formerly often considered opposite processes, more recent evidence suggests a common underlying neurobiological system (Fields, 2006; Le Magnen et al., 1980; Leknes and Tracey, 2008). An example of where pain and pleasure directly interact on a neural level is reward related analgesia where anticipation or acquisition of a reward diminishes pain (Fields, 2006; Leknes and Tracey, 2008).

One underlying system playing a crucial role in pain regulation as well as reward processing, is the endogenous opioid system (Fields, 2004; Fields and Margolis, 2015; Leknes and Tracey, 2008). The discovery of the endogenous opioid system is relatively recent, the use of opium however can be traced back to Sumerians in 3000 BC. Morphine, the most active ingredient of opium, is still a universally used painkiller despite side effects including respiratory depression, dependence and tolerance (Merrer, 2009). Opiates such as morphine and heroine do not only have pain relieving properties but can also generate strong appetitive motivational actions and do have addictive potential (Fields, 2004). The role of the opioid system in addiction and its potential in the treatment of pain conditions made especially the mu-opioid receptor (MOR) system a target for medical research.

Early animal research indicated a promising role for opioid modulation in other areas than pain, such as social bonding (Herman and Panksepp, 1978; Panksepp et al., 1978) and threat learning (Good and Westbrook, 1995; McNally, 2009; McNally and Westbrook, 2003). Human research supports these findings, suggesting a key modulatory role for the MOR system in human social-emotional behavior and processing, which is especially relevant with regard to the current opioid crisis in North America. Crucially, evidence points towards an inhibitory role of the MOR system in the attention allocation to-, processing, and acquisition of threat related associations (Bershad et al., 2016; Eippert et al., 2008; Haaker et al., 2017; Ipser et al., 2013; Løseth et al., 2018) and further, indicates that opioid modulation affects the hedonic processing of social reward (Buchel et al., 2018; Chelnokova et al., 2014; Eikemo et al., 2017, 2016). Opioid modulation of both social threat and reward is not only relevant from a perspective of fundamental research with regard to its role in healthy social functioning (including emotion regulation, motivational processes and social bonding), but also with respect to clinical implications. Experience of early childhood adversity is related to long-term changes in endogenous opioid functioning and increased vulnerability for addiction and mood disorders later in life (Kennedy et al., 2006; Savulich et al., 2017). Further, a high comorbidity has been reported between long-term opioid use and increased anhedonia, pain and anxiety (Garland et al., 2019).

With the recent increase of attention to the role of the MOR system in human social-emotional behavior, the current paper examines the stand of research from the perspective of an opioid

mediated continuous reinforcement model of social behavior. In short, if an individual experiences chronic stress or trauma during their life, opioid modulation of social behavior might shift from reinforcing actively social- to socially-avoidant behavior, characterized by altered sensitivity to reward, pain, threat and stress.

From Pain and Pleasure to Social Behavior

The Motivation-Decision Model of Pain (Fields, 2006) states that through unconscious decision processes, anything that has higher relevance for survival than pain receives action preference over pain related reflexes and therefore is potentially inhibiting nociception. This allows for an adequate response to environmental stimuli that require attention. Therefore, a salient reward cue may activate antinociceptive effects in the descending pain modulatory system and produce pleasure related analgesia allowing for reward pursuit. The second important environmental cue that can potentially gain action preference above pain reflexes as well as reward driven behavior is threat. Threat-perception may lead to stress induced analgesia (Ribeiro et al., 2005), enabling the individual to respond effectively to potential danger in their environment.

Both these processes are known to be driven by opioid modulation (Fields, 2006; Leknes and Tracey, 2008; Rebouças et al., 2005; Szechtman et al., 1981) through mediation of the hedonic value of affective cues. This in turn can promote goal directed approach-avoidance behaviors allowing for pain and threat avoidance as well as the pursuit of reward. Indeed, enhancing mu-opioid activity by administration of an opioid agonist (see Table 1 for a for this review relevant overview of MOR system agonists and antagonists), can increase pleasantness for different reward stimuli (Eikemo et al., 2016), as well as decrease aversiveness of negative experiences such as pain (Fields, 2004). Blocking the mu-opioid system, on the other hand, results in decrease of pleasurable experience from rewards (Buchel et al., 2018; Chelnokova et al., 2014; Eikemo et al., 2016) and disrupts placebo- and reward induced analgesia (Rutgen et al., 2015). Importantly, either of these affective experiences are linked to changes in opioid activity in brain structures involved in social-emotional processing such as the amygdala, the periaqueductal gray (PAG), the orbitofrontal cortex (OFC), the nucleus accumbens (Nacc) and the ventral pallidum (VP) (Buchel et al., 2018; Leknes and Tracey, 2008; Ribeiro et al., 2005). Recent animal and human research provide evidence that this function of the MOR system extends from such basic approach-avoidance mechanisms to more complex social behavior. Through the modulation of hedonic value the MOR system indirectly influences motivational aspects and emotional learning which in turn drive more complex social behaviors such as social rejection, empathy, anxiety, bonding and touch (Eippert et al., 2008; Haaker et al., 2017; Hsu et al., 2013; Nummenmaa et al., 2016; Rutgen et al., 2015). An increasing number of studies investigate the influence of opioid modulation on these social-emotional behaviors, which we will review in the upcoming paragraphs.

Table 1.

Selected overview of mu-opioid receptor agonists and antagonists

Drug	Type	Binding mechanisms
Morphine	Agonist	Opioid agonist with high affinity to the mu-opioid receptor and lower affinity to kappa- and delta-opioid receptors in the CNS.
Buprenorphine	Agonist	Partial agonist to the mu-opioid receptor and antagonist to the kappa-opioid receptor in the CNS.
Naltrexone	Antagonist	Competitive opioid antagonist with high affinity to the mu-opioid receptor and lower affinity to kappa- and delta-opioid receptors in the CNS.
Naloxone	Antagonist	Competitive opioid antagonist with high affinity to the mu-opioid receptor and lower affinity to kappa- and delta-opioid receptors in the CNS.

Overview of a selection of MOR agonists and antagonists and their binding mechanisms to the three opioid receptor types (mu, delta and kappa opioid receptors). The selection is based on information relevant to understand the described research in this paper. CNS = central nervous system.

Social rejection and empathy

Neuroimaging evidence demonstrates that social pain, defined as the experience related to the damage or loss of close social relationships or a self-devaluation through rejection or negative evaluation, shares the neural underpinnings of physical pain (Eisenberger, 2012; Eisenberger and Lieberman, 2004). From an evolutionary perspective, social pain is suggested to have derived from the neural mechanisms of physical pain, motivating individuals to increase their chances of survival by avoiding social isolation and creating strong social bonds (Cacioppo and Hawkley, 2009). The pain of social rejection has been associated with increased MOR activity in areas of the brain considered part of the physical pain modulation circuitry (cf. Fields, 2004), including the bilateral amygdala, midline thalamus, the subgenual anterior cingulate cortex (sgACC) and the right ventral striatum (Hsu et al., 2013). Crucially, administration of buprenorphine reduces perceived social rejection in humans (Bershad et al., 2016) and separation distress is decreased after morphine administration and increased after naloxone administration in rodents (Herman and Panksepp, 1978). Moreover, increased MOR activity in areas involved

in pain processing during rejection is not only related to reduced feelings of rejection, but also with increased resilience traits (Hsu et al., 2013), thus serving a protective function.
A recent study gave first insight into the underlying opioid driven neurochemical base of empathy for pain (Rutgen et al., 2015). The authors demonstrated that administration of naltrexone compared to placebo, did not only block the effect of placebo analgesia on self-perceived pain as one could expect, but crucially, also reduced the effect of placebo analgesia on other-perceived pain (Rutgen et al., 2015). Thus, beyond a shared neural network for pain and social pain, a common opioid centered neurobiology seems to modulate physical pain, social pain and empathy for pain.

Fear and Stress

Similar to the adequate response to pain, adaptive responses to threat and stress are important to assure safe navigation and health in our everyday life. Key brain structures involved in threat processing, including the nuclei of the amygdala, thalamus, ACC and PAG are densely innervated with mu-opioid receptors and suggested to be involved in opioid mediated modulation of anxiety (McNally et al., 2004; Poulin et al., 2006). Evidence from rodent research indicates an inhibitory role for endogenous opioids in the acquisition of threat associations and further a facilitatory role for unlearning such associations. Indeed, administration of MOR agonists decrease efficacy of threat conditioning whereas administration of opioid antagonists enhance threat conditioning and disrupt extinction (Good and Westbrook, 1995; McNally et al., 2004; McNally and Westbrook, 2003; Westbrook et al., 1991).
In humans, the endogenous MOR system can also inhibit the acquisition of conditioned threat associations (Eippert et al., 2008; McNally, 2009), since blocking the MOR system resulted in enhanced processing in pain and threat-related pathways, including the amygdala, rostral ACC and PAG and enhanced behavioral conditioned responses (Eippert et al., 2008). Crucially, these findings were recently extended towards social learning as threat conditioning through observational learning was sustained after naltrexone administration as reflected by enhanced stress responses in the amygdala, midline thalamus and PAG (Haaker et al., 2017). These results thus support the idea that the MOR system shapes aversive learning based on first-hand as well as indirect, social experiences (Eippert et al., 2008; Haaker et al., 2017).
Social perception studies in humans support this idea. Blocking the mu-opioid system with naltrexone resulted in an attentional bias to emotional faces and an increased identification of the emotional expressions anger and happiness (Wardle et al., 2015), emotions that are known to evoke approach motivation. This bias to detect socially relevant information is in line with the notion of Panksepp's BOTSA (Panksepp et al., 1978), that blocking the MOR system leads to emotional distress and subsequently results in behaviors that lead to social support and protection from potential threat. Administration of buprenorphine decreases the attentional bias for fearful faces (Bershad et al., 2016) and reduces fear recognition sensitivity (Ipser et

al., 2013). Moreover, administration of the MOR agonist morphine decreases the subjective perception of anger in ambiguous as well as neutral faces (Løseth et al., 2018). In line with this protective role of mu-opioid activity in social threat perception, a recent study showed that buprenorphine also reduces the subjective perception of social stress, as well as the cortisol stress-response, which translates results so far only obtained in rodents (Bershad et al., 2015; Drolet et al., 2001; Ribeiro et al., 2005; Valentino and Van Bockstaele, 2015). This mechanism most likely underlies the observation that MOR activity can promote immediate anxiolytic and analgesic responses in humans after a traumatic event which is comparable to the analgesic response to inescapable shocks in animals (van der Kolk et al., 1985).

Overall, the reviewed evidence suggests a protective role of the MOR system in response to threat, pain or stress through dynamic regulation of psychological, physiological and endocrine responses. However, even though the protective, stress reducing effects of the MOR system are adaptive in the short-term, chronic exposure to stress can result in dysregulation of opioid mediated stress mechanisms that creates a shift toward MOR inhibition leading to tolerance and dependence – comparable to the effects of substance abuse (Valentino and Van Bockstaele, 2015). Indeed, early childhood adverse experiences are associated with altered reward processing and increased vulnerability to substance abuse disorders (Andersen and Teicher, 2009; Cohen and Densen-Gerber, 1982; Enoch, 2011), through dysregulation of opioid functioning (Gustafsson et al., 2008). Such dysregulation could in turn play an important role in psychopathologies such as PTSD, depression or (social) anxiety. These psychopathologies are related to hyper-reactivity of neural networks linked to social rejection and decreased reward responsivity (Lutz et al., 2018; Lutz and Kieffer, 2013a; Ribeiro et al., 2005). Similarly chronic opioid use can result in anhedonia and deficits in emotion regulation (Garland et al., 2019, 2017). Repeated confrontation with aversive social experiences can alter the sensitivity to social cues in the long-term through a similar shift in opioidergic mechanisms, towards increased sensitivity for negative social cues and dampened responding to positive social stimuli. Thus, although the protective, stress reducing effects of the MOR system are adaptive in the short-term, chronic exposure to stress can deplete this protective function, resulting in hyper- and hypo-reactivity of opioid-dependent neural networks.

Social reward, bonding & affiliation

We previously described the behavioral and underlying neural connection between the processing of rewarding and painful stimuli, with the indication that the MOR system is involved in attributing the hedonic value to pain and reward. Looking specifically at the processing of reward cues, research in rodents localized ‘hedonic hotspots’ in the brain reward circuitry. The rostrodorsal shell of the Nacc and the caudal ventral pallidum (VP) have been identified as the mu-opioid hotspots for the hedonic ‘liking’ of reward (Berridge and Kringelbach, 2013;

Peciña et al., 2006). Research on social play, a social behavior which is intrinsically rewarding, highly important for social and cognitive development and crucial for peer-bonding, has been shown to be mediated by the MOR system (Guard et al., 2002; Trezza et al., 2010; Vanderschuren et al., 1995). Additionally, it has been suggested that the MOR system is involved in the motivational component of reward approach behavior, therefore, increasing the wanting of rewards. More specifically, the mu-opioid system might contribute to the motivation to obtain reward cues, since, after mu-opioid agonism in the medial Nacc shell, animals showed to work harder for food reward (Peciña, 2008; Zhang et al., 2003).

These findings, on the one hand, are important to understand addiction behaviors, but on the other hand have also great relevance for research on appetitive responses to social interaction and affiliation mechanisms. The brain opioid theory of social attachment (BOTSA), which was developed on the basis of groundbreaking work from infant-attachment studies, indeed suggests such a central role of the MOR system in bonding and attachment (Panksepp et al., 1980). Human research so far, supports the idea that the MOR system is involved in the hedonic, and to a lesser extent motivational, aspects of social reward behavior. A recent neuroimaging study (Buchel et al., 2018) found a specific effect of MOR blockage on the hedonic value of reward in both, pleasure ratings and reward related neural activation in the ventral striatum, lateral orbitofrontal cortex, amygdala, hypothalamus and medial prefrontal cortex, however no effect on reward anticipation. Chelnokova et al. (2014) explored the question whether the MOR system is involved in the hedonic as well as motivational aspects of social reward directly, using a behavioral task assessing the 'liking' and 'wanting' of attractive faces. Interestingly they found that administration of the MOR agonist morphine increased specifically the liking of stimuli with high reward value, whereas blocking the mu-opioid system with naltrexone specifically decreased the liking of such. In line with the idea that the hedonic value influences the motivational component of reward, participants also invested more effort to keep seeing highly attractive stimuli under morphine but lessened their effort with naltrexone. Blocking the MOR system additionally increased the effort to stop viewing images that participants perceived low in reward value (Chelnokova et al., 2014). Further, it is reasonable to assume that with such an increase of the hedonic value of, as well as motivation for, reward stimuli, these are also better remembered. Looking at memory of social reward cues such as happy faces, administration of buprenorphine compared to placebo was indeed followed by a significant increase in memory for happy faces compared to other emotions (Syal et al., 2015). Based on the idea that social affiliation is at least partly driven by basic reward mechanisms, several studies support the idea of BOTSA (Herman and Panksepp, 1978; Panksepp et al., 1980), that the mu-opioid system plays an important role in supporting the formation and maintenance of social affiliation. For example, in human subjects we recently showed an increase of automatic facial responses associated with negative emotions (anger, sadness) in response to happy faces (Meier et al., 2016). Happy faces are considered powerful social

reward cues and automatic imitation of happy facial expressions has been shown to promote social affiliation. We therefore suggested that blocking the MOR system disrupts the automatic behavioral response involved in social bonding (Meier et al., 2016). A study using positron emission tomography found an increase of MOR activation in response to social acceptance in areas related to reward and social salience processing, namely the ventral striatum, amygdala and insula. In addition, MOR activation in the ventral striatum was predictive for higher desire of social interaction (Hsu et al., 2013). Likewise, the feeling of (interpersonal) warmth, part of the pleasurable feelings related to social bonding, has also been associated with MOR activity in humans (Depue and Morrone-Strupinsky, 2005). Schweiger et al. (2013), found that warmth-liking can induce trust, but that administration of naltrexone decreases warmth-liking. Interestingly, two further studies found that blocking the MOR system with naltrexone specifically decreased the feeling of social connection associated with warmth-liking, without modulating other affective (pleasantness etc.) or sensory component (Inagaki et al., 2015, 2016).

Taken together, the MOR system seems to promote the hedonic and motivational components of social reward, which in turn drives memory and decision-making towards the facilitation of social bonding and affiliation. Of interest, however, is that patients with long-term prescriptive opioid use, and especially opioid mis-users, show attenuated attentional and autonomic responses to natural rewards (e.g. food stimuli), and deficits in emotion processing (Garland et al., 2017, 2015; but see Eikemo et al., 2019). Dysregulation of opioid mediated reward mechanisms, for example through experience of chronic stress, as described earlier in relation to fear and stress, may thus lead to a reduction in the experience of pleasure and decrease the sensitivity to social cues that create opportunities to experience positive social interactions (Hsu et al., 2013; Inagaki, 2018; Meier et al., 2016).

Touch

A fundamental behavior implicated in social reward and relationship maintenance, in non-human primates as well as humans, is touch. Primate research showed that grooming, next to its function in hygiene, seems to be highly relevant for the formation and maintenance of social bonds (McGlone et al., 2014). In humans, touch has been shown to be a crucial factor in infant development (Field, 2010), it functions as safety signaling in parent – children interactions (Brummelman et al., 2018), and generally acts as a social buffer by reducing stress and altering the perception of pain and threat (Coan et al., 2006; Morrison, 2016). The mu-opioid system is suggested to mediate the positive effects of touch (Weller and Feldman, 2003). Research in non-human primates clearly shows modulation of grooming behavior through opioid mechanisms (Keverne et al., 1989). However, the fact that the animals are housed socially or isolated at different stages of these experiments makes a straightforward interpretation of the results difficult since the motivational state of the animal at time of drug administration

might influence the measured outcome (c.f. Loseth et al., 2014). A study by Martel et al. (1993) showed that socially housed monkeys displayed gradually less grooming behavior towards their infant with naloxone administration over several weeks. Social grooming between adults decreased instantly from the first administration of naloxone. This suggests a certain amount of variability in the role of opioid modulation in mother-infant attachment and adult relationships and the relevance of touch therein (e.g. additional role of oxytocin in mother-infant attachment).

There is relatively little human evidence investigating the role of the mu-opioid system in touch. In one study, 20min of mother-infant skin-to-skin contact showed to reduce the peripheral levels of cortisol and beta-endorphins in the blood samples of the infants, presumably due to a decrease of hypothalamic-pituitary-adrenal axis activity (Mooncey et al., 1997). Nummenmaa et al. (2016) found deactivation of endogenous mu-opioid activity during social touch compared to a non-social control condition, in areas of social reward and affective processing (ventral striatum, amygdala, medial prefrontal, and orbitofrontal cortex). Their findings however are contradictive to other evidence in humans and animals (Case et al., 2016; Keverne et al., 1989; Løseth et al., 2019; Martel et al., 1993; Mooncey et al., 1997). Finally, a study investigated the role of the mu-opioid system in perceived affective touch (activates C-tactile fibers in the skin which are suggested to mediate the pleasantness of touch) in healthy adults and patients with fibromyalgia (Case et al., 2016). Fibromyalgia is a chronic pain condition which has been related to decreased central MOR availability. Whilst in healthy participants MOR blockade with naloxone resulted in increased pleasantness ratings for touch, patients with fibromyalgia showed decreases in touch intensity ratings but no alteration of touch pleasantness (Case et al., 2016). On the other hand, a recent experimental study found no evidence for opioid modulation of c-tactile fiber mediated touch pleasantness, nor for the motivation to receive touch, after administration of morphine or naltrexone (Løseth et al., 2019). It is important to consider though that the application method of c-tactile optimal touch in the experimental context does not represent social, affiliative touch, nor is it a social buffering context, and might therefore not be opioid mediated (Ellingsen et al., 2016; Løseth et al., 2019). As an example for social buffering, Coan et al. (2006) showed that hand-holding between partners reduced negative affect and neural activation to the threat of physical pain, which speaks for opioid regulation of these effects.

In sum, there might be a role for the MOR system in touch. However, more research is warranted given the subjectivity and sensitivity of touch to context, as well as the variety in methods and measurements used in a range of different studies. Given that research on social reward showed that the MOR system might specifically reinforce positive social cues, future research should integrate the social aspect as a crucial component when investigating the interaction between MOR regulation and touch.

A mu-opioid feedback model of social interaction

Based on the reviewed evidence of the acute effects of opioid agonists and antagonists on human social-emotional behavior, we propose a mu-opioid feedback model of social interaction (Fig. 1). The model places opioid modulation of social pain, threat and reward processing in a theoretical framework of social behavior, suggesting an interactive role for MOR system in supporting affiliative or protective social motives through changes in neural sensitivity and behavior. Further, the model takes into account translational evidence on mechanisms and consequences of early trauma and chronic stress, which might be cause to a change in sensitivity to opioids that is comparable to substance abuse. The main purpose of this model is to provide a heuristic framework based on current evidence, to help disentangle complex opioidergic mechanisms of social-emotional behavior and therewith facilitate development and testing of new hypotheses.

On the one hand, the MOR system is a driving factor in building and strengthening our social connections. Panksepp et al. (1980) proposed that the role of the MOR system in social attachment behaviors could have developed from basic pain regulation systems that initiate behaviors which increase chances of survival. For example, distress vocalizations in young animals assure closeness and attention by their mother. Evidence for this hypothesis was collected on the basis of infant attachment behavior, where social distress could be relieved or induced by administration of MOR agonists or antagonists respectively (Herman and Panksepp, 1978; Panksepp et al., 1978). In humans, the limited neuroimaging evidence available shows that perception of rewarding social cues has been associated to mu-opioid mediated activity in mesocorticolimbic structures (ventral striatum, lateral OFC, amygdala, hypothalamus, mPFC) (Buchel et al., 2018), with MOR activity in the ventral striatum after a positive social experience being predictive for interest in social interaction (Hsu et al., 2013). Therefore, if an individual interprets a social experience as positive through integration of social cues, context, etc., endogenous mu-opioids are released in areas related to reward processing, mediating the pleasant hedonic experience of social interaction. On a secondary level MOR activity decreases the individual's sensitivity for negative social cues and increases sensitivity for social reward cues (Ipser et al., 2013; Løseth et al., 2018; Syal et al., 2015). On a behavioral level this creates a positive feedback loop, resulting in increased social exploration and active affiliative behavior, creating space for additional positive social interactions due to positive anticipation of social reward cues. In the long-term, if an individual accumulates positive social experiences it leads to facilitation of strong long-term bonds with others which enacts as a strong social buffer in stressful situations (Machin and Dunbar, 2011) (Fig. 1A).

When encountering negative social cues that elicit a stress response, the release of opioids has a protective role which equally has been suggested to originate from pain regulatory mechanisms. In this case the pain regulatory mechanisms are aimed at decreasing painful experiences and eliciting behaviors associated with reacting to-, coping with-, and anticipation of poten-

tially threatening events (Fig 1A). On a more complex social-emotional level opioids allow to modulate the behavioral response to social pain, stress and fear, which protects against negative affect, also when seeing others in distress and therewith possibly, similar to oxytocin (Bos et al., 2015), facilitating helping behavior (Bershad et al., 2016, 2015; Haaker et al., 2017; Hsu et al., 2013; Nummenmaa and Tuominen, 2017; Rutgen et al., 2015). Therefore, if an individual experiences an aversive social situation, MOR activity increases in areas related to pain and threat related processing including the amygdala, periaqueductal gray (PAG), thalamus, OFC, insula and the Nacc (Haaker et al., 2017; Hsu et al., 2015, 2013; Ribeiro et al., 2005; Zubieta et al., 2001). Moreover, Hsu et al. (2013) showed that greater MOR related activity in this network correlated with greater trait-resilience in the face of rejection, in support of the idea of a protective function of MOR activation. On a subjective level MOR related activity in response to pain is indeed associated with a decrease in sensory responses and negative affect (Zubieta et al., 2001).

This mechanism has however also negative repercussions for social behavior. Indeed, the effects of pain on pleasure and vice versa (Leknes and Tracey, 2008) as well as the effect of stress and cortisol on reward sensitivity (Berghorst et al., 2013; Montoya et al., 2014), indicate that sensitivity for social reward stimuli and therewith associated social exploration are dampened during an acute negative social experience. As previously mentioned, this response is highly adaptive allowing the individual to regulate their social pain and subsequent behavior to create new opportunities for positive social experiences (Fig 1A). The experience of traumatic events or continuous exposure to stress however, leads to a chronic dysregulation of the MOR system resulting in less responsivity to social reward and hypersensitivity to threat, both of these characteristics are strongly associated with social anxiety and depression (Garland et al., 2019; Lutz et al., 2018; Lutz and Kieffer, 2013b; Shurman et al., 2010). Thus, on the biopsychological and behavioral level, the individual enters a self-sustaining negative feedback loop with a strong bias toward anticipation of negative social cues. This bias feeds into the social experience creating a higher possibility of an actual aversive experience whilst reducing the probability of a positive social experience (Fig 1B).

Evidence from the clinical field, for instance that chronic pain as well as prolonged opioid (mis-) use are accompanied by a change in mu-opioid receptor functioning (Garland et al., 2019; Harris et al., 2007; Jones et al., 1988; Klega et al., 2010), reduced reward sensitivity and attenuation of emotion regulation capacities (Garland et al., 2017, 2015), and that early childhood trauma and PTSD increase vulnerability to addiction and mood disorders (Kennedy et al., 2006; Malcolm-Smith et al., 2013; Savulich et al., 2017), supports this line of thought. Further, research on the consequences of opioid use during pregnancy indicate a dysregulation of the central and autonomic nervous system in newborns with Neonatal Abstinence Syndrome (NAS), with consequences for basic behaviors such as sleep, feeding, stress reactivity and communication with the parent (Velez and Jansson, 2008). Crucially though, research highlights the importance

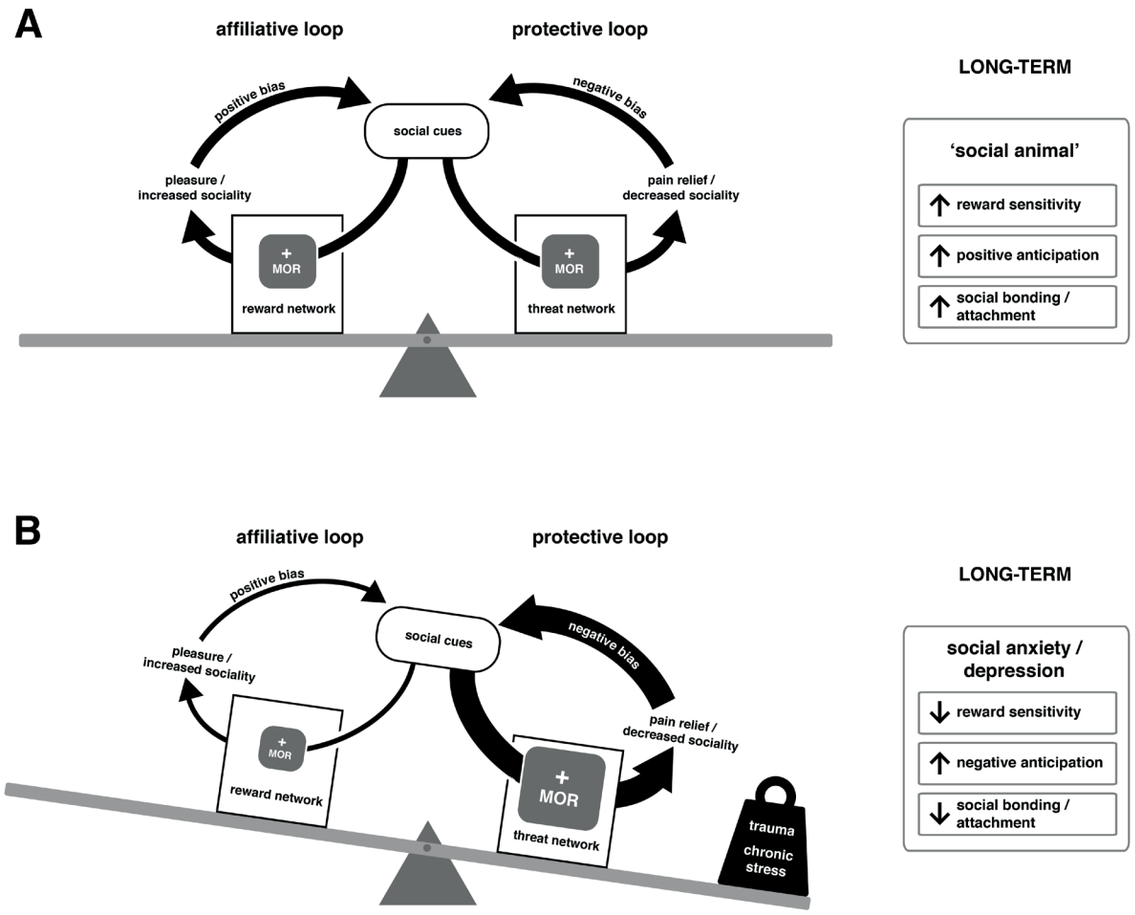

Fig 1. Mu-opioid feedback model of social interaction. When a social interaction takes place, different social cues (e.g. reward, threat) of the interaction itself, including the context, trigger changes in MOR related activity in the brain to generate a hedonic interpretation of the social experience. If the social cue is positive, mu-opioid release in areas involved in reward and emotion processing create a pleasurable hedonic state motivating the individual to invest more time and effort into social interactions (affiliative loop). The individuals' anticipation and reward sensitivity for positive social cues facilitates creating strong social bonds with peers which act as a social buffer in the face of stress. If, on the other hand, the social cue is negative MOR activity in areas related to pain and threat processing help the individual to cope with the acute social pain by inducing pain relieving effects (protective loop). This is highly adaptive, it gives the individual time to regulate their behavior adequately to the situation and if necessary, to recover from the experience, but it also results in acutely decreased social reward sensitivity and social exploration. Dynamic shifts between the two loops allow for flexible behavior and a continuous social learning process, leading in the long-term to the well-adjusted 'social animal' (A). If the individual is confronted with frequent negative, potentially traumatic experiences, long-term changes in the neuro-chemical set-up of the MOR can create a shift in behavioral patterns toward the protective loop. The shift is characterized by chronically reduced sensitivity for social reward cues and an increase in anticipation for negative social cues such as threat or fear cues. This behavioral pattern makes it increasingly difficult to engage in future positive social interactions potentially leading to insecure attachment and difficulty to form strong long-term bonds (B). +MOR: change in mu-opioid receptor activity.

of contextual factors, such as quality of caregiving or stability of the social environment, in the long-term development of these infants (Sarfi et al., 2011). Therefore, whilst pre-natal opioid exposure represents a heightened vulnerability and risk factor, quality of caregiving, and therewith early exposure to a stressful or secure environment, is a crucial predictor for attachment, resilience and development.

Clinical relevance

The reviewed evidence on social behavior and emotional processing gives reason to consider the role of opioids in clinical context, especially with regard to psychopathologies where changes in the ability to perceive pleasure or process threat are part of the symptomatic, such as social anxiety and depression (Colasanti et al., 2011; Lutz et al., 2018; Shechner et al., 2012).

In line with the idea of a protective role of MOR activity, research suggests that opiodergic neurotransmission is involved in anxiolytic responses by dampening negative affect and distress in an acutely stressful situation (Colasanti et al., 2011), which might be dysregulated in the case of social anxiety. Characteristics of social anxiety include hypersensitivity to threat and dampened social reward sensitivity (Shechner et al., 2012). As previously reported, pre-clinical as well as human experimental work clearly demonstrate a role for the mu-opioid system in fear learning (Eippert et al., 2008; Good and Westbrook, 1995; Haaker et al., 2017; McNally, 2009; Westbrook et al., 1991) and reward processing (Berridge and Kringelbach, 2008; Chelnokova et al., 2014; Peciña et al., 2006; Syal et al., 2015), therefore the MOR system could contribute to symptoms of social anxiety by changing sensitivity to threat and reward cues.

A distinct characteristic of depression is the decreased ability to perceive pleasure, which can be termed as reduced reward responsivity and increased sensitivity to social pain (Lutz et al., 2018). Neuroimaging evidence indicates that individuals with depression show an elevated MOR tone in the thalamus during baseline measurements, and they further lack the MOR deactivation in rostral ACC, ventral pallidum, amygdala and inferior temporal cortex in response to a sustained state of sadness that was found in healthy controls. Rather they showed an increase of MOR related activation in the inferior temporal cortex (Kennedy et al., 2006; Zubieta et al., 2003). In addition, individuals with depression show a decreased MOR response in response to direct social rejection and they lacked the MOR mediated reward response in the Nacc that healthy controls showed (Hsu et al., 2015).

A further point to consider in this context is that the MOR system has a direct impact on the HPA axis, which plays a major role in aversive learning processes. Animal work, looking at the interactive role of the MOR system and corticotropin releasing factor (CRF) in the locus coeruleus, suggests a protective role of the MOR system with the occurrence of acute stressors, downregulating the effects of CRF and therewith promoting recovery after the stressor.

Repeated stress however has been shown to shift the balance in the locus coeruleus toward inhibitory MOR regulation, resulting in long-term modifications of neural circuits supporting evidence of a link between post-traumatic stress disorder (PTSD) and vulnerability for substance abuse (Valentino and Van Bockstaele, 2015). The results are further in line with research suggesting that childhood trauma results in long-term changes in the mu-opioid system, accompanied by altered emotion regulation mechanisms, as well as heightened vulnerability for substance abuse and mood disorders later in life (Kennedy et al., 2006; Malcolm-Smith et al., 2013; Savulich et al., 2017), and adds to neuroendocrine models that explain how childhood adversity affects social-emotional behavior and impaired quality of caregiving in later generations (Bos, 2017)

Future directions

Research up to date clearly indicates a role for the mu-opioid system in a range of social behaviors. At the same time, looking at the reviewed evidence human research is only at its beginning. On a methodological level the reviewed research outlines the importance of translational research and designs to build strong, more causally conclusive evidence. In addition to what has been done so far, the use of physiological measures such as eye-blink startle-reflex, facial electromyography or eye-tracking could contribute valuable implicit behavioral data. A continued issue is the non-standardized use of drug dosage in administration studies, as well as the fact that some of the agonists and especially all of the antagonists used do not have exclusive affinity to mu-opioid receptors. In future research, more well-powered studies including both, agonist and antagonist manipulation, are necessary to make conclusions on a bidirectional level.

Next, based on the proposed mu-opioid feedback model of social interaction we will suggest research questions from two different angles to be investigated in the future, starting with a fundamental research perspective, followed by a consideration of the effects of trauma and chronic stress. Our model proposes, on the basis of existing experimental research, that the MOR system modulates the sensitivity to social threat and reward, and crucially also learning processes related to threat and reward cues that drive more complex social behavior.

To begin with, several fundamental research questions remain unanswered. Human studies demonstrated an inhibitory role for the MOR system in the acquisition of threat related associations (Eippert et al., 2008; Haaker et al., 2017). With regard to threat related mechanisms, generalization of fear to cues to neutral or safe stimuli is a common phenomenon in anxiety and PTSD (Lissek et al., 2008) and considering the MOR system's role in fear conditioning it is likely that opioids contribute to threat memory formation. As a first suggestion, we hypothesize that the MOR system inhibits generalization of fear cues to other modalities. At the same time rodent research suggests a facilitatory role of mu-opioid modulation in threat extinction

learning (McNally, 2009; McNally and Westbrook, 2003). Threat extinction is a crucial emotion regulation strategy which is often impaired in mood disorders such as anxiety or PTSD. We therefore suggest that it would be timely to test whether the MOR system also facilitates threat extinction in humans.

Next, in the context of social reward, animal and human research indicate that the MOR system is important for both the hedonic value and the motivational aspect of reward (Chelnokova et al., 2014; Eikemo et al., 2017; Peciña, 2008). At the same time, Buchel et al. (2018) found that the hedonic component is opioid dependent, whereas reward anticipation is not. In our model we suggest that by modulation of reward (and threat) sensitivity a bias toward new social cues is created, influencing both anticipation and the motivational aspect to engage with these. To disentangle further, to what extent endogenous opioids contribute to 'wanting' of reward and whether these mechanisms are dopamine dependent, it would be valuable to study the interaction of dopamine and endogenous opioids in reward processing and motivation using joint administration of a MOR agonist with a dopamine antagonist.

Moreover, considering the crucial role of the MOR system in pain – reward processing and the regulation of both, looking at opioid modulation approach – avoidance mechanisms could contribute interesting data in disentangling the mu-opioid system's role in social-emotional functioning. Unpublished, preliminary work of our own suggests that blocking the MOR system resulted in heightened threat reactivity in a context that allowed for threat avoidance. With approach-avoidance characterizing both appetitive motivation as well as fear of punishment, previous research (Terburg et al., 2011, 2012; Terburg and van Honk, 2013) has made the link to social dominance which is related to high reward drive and reduced anxiety related behaviors. With the mu-opioid release being involved in the increase of specifically high reward liking and evidence showing MOR agonist administration results in a decrease of perceived anger (Løseth et al., 2018) and other threat cues (Bershad et al., 2015; Ipser et al., 2013), future research should investigate whether the MOR system facilitates dominant behavior in social contexts.

Finally, within the framework of the proposed mu-opioid feedback model of social interaction and the reviewed evidence from rodent and human literature, investigating the mu-opioid modulation of acute and chronic stress seems promising. From a fundamental perspective it would be interesting to start with testing in humans whether stress-induced analgesia is opioid dependent. Next, considering the proposed mu-opioid feedback model of social interaction, it would be timely to investigate whether differences in threat and reward processing in individuals who have experienced early trauma or chronic stress are opioid mediated. Evidence from such research would not only be informative regarding the efficacy of opioid mediated pain regulation in different populations, but could contribute knowledge about a biological mechanism underlying the psychological processing of traumatic events and the persistence of automatic behavioral tendencies that contribute to symptomatic of affective disorders (e.g. PTSD, social anxiety).

Conclusion

With the MOR system being an underlying factor of the continuous, competitive regulation of pleasure and pain, it is crucial to investigate its role in social-emotional behaviors as it contributes to our ability to respond in an adaptive manner to social experiences. Based on existing evidence we propose a mu-opioid feedback model of social interaction which suggests a distinct role of the MOR system for regulating affect and behavior in social interactions and takes into account long-term consequences for social behavior and health. In an acute social interaction, the MOR system creates a hedonic interpretation of the experience which triggers a neurobiological and behavioral response that either serves affiliative purposes or helps to protect from negative experiences. In the short term the protective response to negative experiences is highly adaptive. With chronic exposure to stress though, long-term changes in the MOR neuro-chemical set-up can create a shift in behavioral patterns with implications for social anxiety and depression. Our proposed model is an attempt to provide a theoretical framework of opioid modulation of social-emotional behavior, based on which new hypotheses can be formed and tested.

Chapter 3

Naltrexone increases negatively-valenced facial responses to happy faces in female participants

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Psychoneuroendocrinology (2016)

Abstract

Positive social cues, like happy facial expressions, activate the brain's reward system and indicate interest in social affiliation. Facial mimicry of emotions, which is the predominantly automatic and unconscious imitation of another person's facial expression, has been shown to promote social affiliation. It has been demonstrated repeatedly that the opioid system is vital to social affiliation in rodents, but there is less evidence in humans. We investigated whether a 50mg administration of naltrexone, an opioid antagonist with highest affinity for the mu-opioid system, modulates emotional mimicry. A passive viewing task with dynamic facial expressions was used in a randomized placebo controlled between-subjects design. Mimicry was measured with electromyography (EMG) on three facial muscles, the corrugator supercilii and the depressor jaw muscle, associated with negatively-valenced emotions, and the zygomaticus major, which is activated during smiling. The results demonstrate an increase of negatively-valenced facial responses (corrugator and depressor) to happy facial expressions after naltrexone compared to placebo, consistent with lowered interest in social interaction or affiliation. Our findings provide evidence for a role of the opioid system in modulating automatic behavioral responses to cues of reward and social interaction, and translate to rodent models of the mu-opioid system and social affiliation.

Introduction

Social affiliation processes, the formation of strong emotional bonds with individuals in our social environment, are crucial in our everyday life. The absence of positive social contact and isolation has been shown to negatively affect health and well-being (Cacioppo et al., 2015). A pivotal social reward cue that signals interest in social affiliation, indicates social approval and that has been shown to activate the brain's reward system, is happy facial expressions (Spreckelmeyer et al., 2009). Facial mimicry, the predominantly unconscious and automatic activation of facial muscles in response to emotional expressions (Dimberg et al., 2002), towards happy faces has been referred to as 'social glue', due to its properties of promoting affiliation and binding individuals together (Hess and Fischer, 2014; Lakin et al., 2003). Congruent facial mimicry can therefore be considered a measure for social affiliative behavior in humans.

The opioid system represents one of the underlying neurobiological factors of social affiliation. The attractiveness and pursuit of a rewarding stimulus is driven by several aspects: the motivational 'wanting' of the reward, the hedonic 'liking' of the reward and the associative 'learning' of the context in which a reward cue appears. The opioid system has been shown to especially contribute to the hedonic value ('liking') of rewarding stimuli (Trezza et al., 2011). Further research demonstrated that an increase of 'liking' mediated by the opioid system, may in consequence enhance the motivational 'wanting' of a reward (Syal et al., 2015). Supportive evidence derives from studies demonstrating the role of opioid receptor activity in the nucleus accumbens (NAc), a main structure of the neural reward circuitry, in the attribution of positive value to social interaction in rodents (Trezza et al., 2011) and humans (Hsu et al., 2013). Additionally, in direct relation to affiliative processes, a recent study showed that the mu-opioid system modulates the feeling of social connection in humans (Inagaki et al., 2016).

Naltrexone is an opioid antagonist, which is most selective to the mu-opioid system and which binds competitively at the opioid receptors in the brain (Lee et al., 1988). In the present study naltrexone was administered to investigate if blocking the opioid system would attenuate social affiliative behavioral responses indexed by emotional mimicry to emotional facial expressions. Typically, the zygomaticus major, a muscle that forms a smile by lifting the corners of the mouth, is activated in response to happy faces. The corrugator supercilii, a muscle that produces a frown by drawing the eyebrows together, shows an increase of activation in response to angry faces and a decrease in activation in response to happy faces. The depressor jaw muscle, which pulls the corners of the mouth down is activated for sad faces (Dimberg et al., 2002). Naltrexone was administered in a randomized, double-blind, placebo controlled design. Based on the literature on the opioid system and social affiliation, we expected that naltrexone compared to placebo would disrupt the social affiliative response to happy faces resulting in a decrease in zygomaticus activity. For the depressor activity in response to sad faces two competing hypoth-

eses may be considered. On the one hand, we could expect naltrexone administration to result in an increase of depressor activity, reflecting increased shared pain with others, in line with the potential efficacy of mu-opioids in the treatment of depression (Panksepp and Watt, 2011; Stein et al., 2007). On the other hand, we might expect a decrease of depressor activity in response to sad faces with naltrexone compared to placebo, since mimicry of a sad face can reflect a social affiliative response. From this perspective, a decrease in depressor activity would be in line with our predictions about happy faces, in that blocking the mu-opioid system disrupts socially affiliative responses. Angry facial expressions served as a control measurement.

Methods

Participants

36 female students were recruited at Cape Town University to participate in the study. Only female participants were included because women have been shown to display more robust facial mimicry than men (Dimberg and Lundquist, 1990). Participants were all of South African nationality, Caucasian, right handed, with a mean age of 20.7 years (SD = 2.11), and were screened for any history of psychopathology. Exclusion criteria also contained use of alcohol or painkillers in the last 24 hours, or the general use of psychotropic medication. The experimental protocol was approved by the Human Research Ethics Committee (HREC) of the University of Cape Town, in accordance with the latest declaration of Helsinki. Participants gave written informed consent prior to participation and received payment afterwards.

Drug administration

Either placebo or 50mg of naltrexone, an opioid antagonist, were administered orally, in a randomized, double-blind and counter-balanced manner. Naltrexone has higher selectivity for mu-opioid receptors, compared to kappa- and delta- opioid receptors and is therefore an adequate choice for investigating the role of the mu-opioid system in social affiliation. The mimicry task started 69 minutes after administration and was completed 7 minutes later, to coincide with the central effects of naltrexone (Lee et al., 1988).

Material & Procedure

Upon arrival participants signed informed consent and received naltrexone or placebo in a randomized, double-blind manner. Short video clips of dynamic facial expressions were presented (Hofman et al., 2012) using e-prime version 2.0 (Psychology Software Tools, Pittsburgh, PA) and displayed on a 47cm screen. Participants were positioned 70cm distant from the screen. Before the start of the task, participants were informed that they would see faces with different emotions and instructed to look at the faces, to sit still and move to the head as little as possible, while focusing on the center of the screen. One trial was composed of a fixation cross (1000ms), followed by the dynamic face video clip which was displayed for 3300ms. The video clip in-

cluded 1000ms neutral facial expression (baseline), 1300ms of morphing, with the last frame showing the full emotion expression for 1000ms (cf. Fig1). The inter-stimulus interval lasted 4000ms. All 24 stimuli were displayed twice in a randomized manner, resulting in a total of 48 trials and a task duration of seven minutes. Electromyography (EMG) responses were measured on three muscles, the corrugator supercilii, the zygomaticus major and depressor jaw muscle (cf. Hofman et al., 2012). Ag/AgCl electrodes were used in a bipolar electrode set up (www.biosemi.com). Mood was assessed with a computerized version of the Positive Affect Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, (1988).

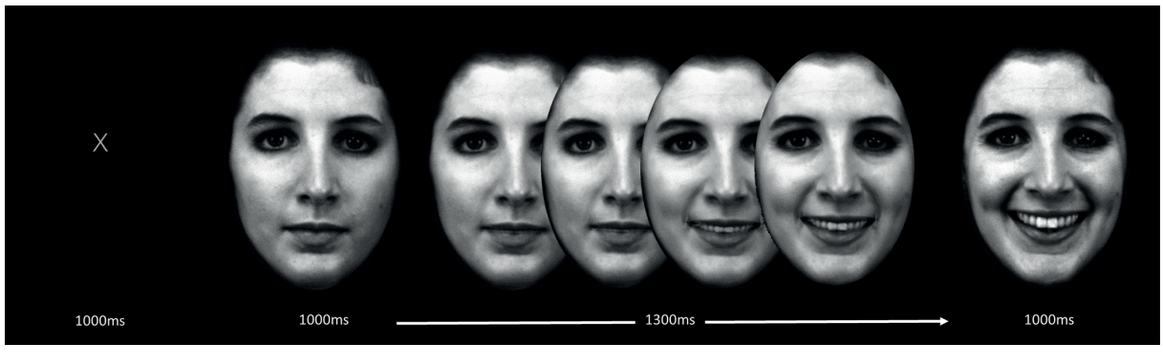

Fig1. Schematic view of a single trial. Fixation cross 1000ms, followed by 1000ms baseline (neutral face), 1300ms of morphing into one of the emotional expressions, which remained on the screen for another 1000ms.

Data reduction and statistical analysis

The electrophysiological data was processed offline with BrainVisionAnalyzer 2.0. Trials were selected -1000ms to +2500ms around the reference marker, filtered, rectified, baseline corrected, and segmented in 14 bins of 250ms per trial (cf. Hofman et al., 2012). The first four bins containing neutral expressions were excluded from statistical analysis. Where sphericity was violated, Huynh-Feldt corrections were applied. In total three participants had to be excluded from analysis, one due to high depression scores and two due to measurement related problems.

Results

Mood and Task Validation

To test for a possible effect of medication on mood ratings, a 2 (naltrexone, placebo) x 2 (positive affect, negative affect) repeated measures ANOVA was performed. There was no effect of medication ($F(1,30)=2.04$, p=.164, $P\eta^2=.06$), nor any significant interaction of mood by medication ($F(1,30)=2.81$, p=.104, $P\eta^2=.09$). We conducted a 3x3x10 (emotion*muscle*time) repeated measures ANOVA in the placebo condition to validate the task. The three way interaction of emotion*muscle*time showed to be significant ($F(5.2, 78.74) = 2.8$, $p = .017$, $P\eta^2 = .16$), as well as the interaction of emotion*muscle ($F(2.9, 43.26) = 5.01$, $p = .005$, $P\eta^2 = .25$). These

interactions show that the muscles responded differently over time to the distinct emotions, thus demonstrating facial mimicry.

Mimicry

A 2x3x10 three-way repeated measures ANOVA (medication*emotion*time) with medication as a between subject factor and emotion and time as within subject factors was conducted per muscle to test for the effect of naltrexone on emotional mimicry.

Corrugator supercilii

There was a significant interaction of emotion*medication on mimicry (F(1.39, 43.1) =3.69, p = .048, $P\eta^2$ = .11) indicating that the corrugator muscle showed a different response to the three emotions depending on drug administrations. There was no main effect of time (F(1.63, 50.6) = .94, p = .383, $P\eta^2$ = .03), nor any interaction of time with emotion and condition (F(2.98, 92.3) = 2.0, p = .120, $P\eta^2$ = .06). The main effect of medication was not found to be significant (F(1, 31) = 2.34, p = .136, $P\eta^2$ = .07).

To break down the interaction, three separate 2x10 (medication*time) repeated measure ANOVAs were conducted per emotion. Results showed a significant main effect of medication for happy faces (F(1,31) = 7.3, p = .011, $P\eta^2$ = .19), but not for angry (F(1,31) = .33, p = .572, $P\eta^2$ = .01) or sad faces (F(1,31) = .03, p = .855 $P\eta^2$ = .001). Crucially, naltrexone administration, compared to placebo resulted in a significant increase in corrugator activity (cf. Fig.2A). The mean activation of the corrugator during happy faces increased from M = -1.36 (SE = 0.3) in placebo condition, to M = -0.24 (SE = 0.29) in the naltrexone condition.

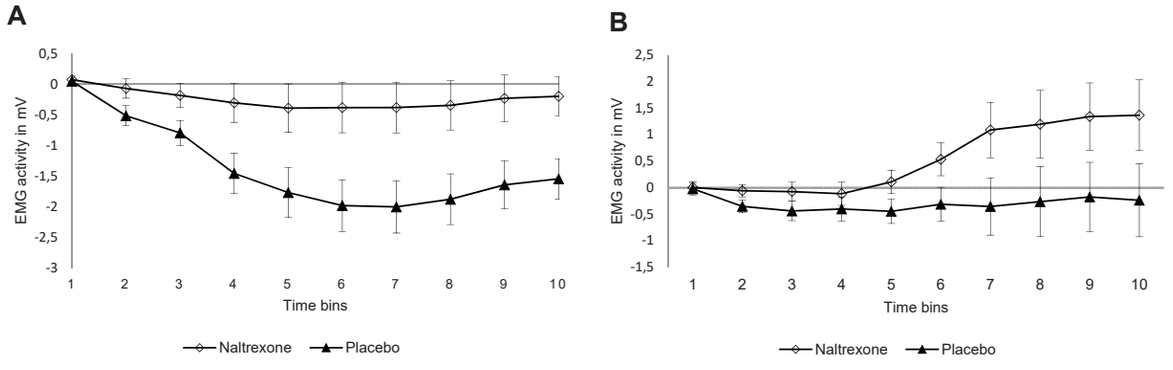

Fig2. Averaged EMG activity in microvolt (mV) of corrugators muscle for happy faces (A) and depressors activity for happy faces (B), over time (bin 1-6 morph; 6-10 full emotional expression). Standard error indicated.

Depressor Jaw Muscle

Trend level effects were shown for both the two way interaction of emotion*medication (F(1.5, 46.4) = 2.63, p = .097, $P\eta^2$ =.08), and the three way interaction of emotion*medication*time (F(2.43, 75.2) = 2.48, p = .080, $P\eta^2$ =.07). The main effect of medication was not significant (F(1, 31) = 0.17, p = .682, $P\eta^2$ =.005). To investigate the effect of medication per emotion, three 2x10 (medication*time) repeated measures ANOVA's were conducted. The analysis showed a near significant effect of naltrexone for the depressor in happy faces (F(1, 31) = 3.93, p = .056, $P\eta^2$ =.11), pointing to an increase of depressor activity after naltrexone administration (cf. Fig.2B). No effect of naltrexone was found for sad (F(1, 31) = 1.06, p = .311, $P\eta^2$ =.03) and angry faces (F(1, 31) = 0.15, p = .705, $P\eta^2$ =.005).

Zygomaticus Major

The ANOVA did not reveal a significant interaction of emotion*medication (F(1.23, 38.1) = .058, p = .859, $P\eta^2$ = .002) nor of emotion*medication*time (F(1.67, 51.7) = .23, p = .759, $P\eta^2$ = .007). Also, the main effect of medication was not significant (F(1, 31) = .02, p = .890, $P\eta^2$ = .001).

Discussion

The literature indicates that congruent facial mimicry in response to happy faces in terms of increased zygomaticus and decreased corrugator activity promotes affiliative interest (Hess and Fischer, 2014). The current findings suggest that naltrexone automatically lowers motivation for social affiliation, as indicated by increased negatively-valenced facial responses (corrugator and depressor activity) to these affiliative facial cues. There was significant increase of activation in the corrugator in response to happy faces during naltrexone, compared to relaxation during placebo, and a near-significant increase of depressor activity for happy faces. The latter findings may correspond to evident negative relationships between opioids and depression, and antidepressant effects of opioid agonist buprenorphine (Panksepp and Watt, 2011). However, while naltrexone increased negatively-valenced facial responses to happy faces, it should be noted that the opioid antagonist did not induce expected decreases of zygomaticus activation for happy faces or increases of activation in the depressor muscle in response to sad faces. In other words, the results demonstrated that by blocking the mu-opioid system, social reward cues like happy faces received greater negative valence.

There are several human studies demonstrating the involvement of the mu-opioid system in motivational and hedonic aspects of social reward behavior (Chelnokova et al., 2014; Syal et al., 2015). The present study extends these findings to social affiliation by demonstrating that the opioid system modulates the automatic, unconscious behavioral response towards rewarding social stimuli like happy faces. Since these positive facial expressions indicate social acceptance and promote affiliative behavior, our findings suggest that mu-opioid antagonism in humans results in reduced affiliative behavior. Our results are also in line with findings indi-

cating that mu-opioid receptor activation in the ventral striatum after positive social feedback is predictive for desire of social interaction in humans (Hsu et al., 2013). Further supporting evidence is provided by the study of Inagaki et al. (2016), which showed that regular intake of naltrexone over 4 days resulted in a decrease in the experience of social connection, on the basis of daily reports and in a laboratory setting.

As a limitation to the present study it must be mentioned that the effect on the depressor was only near significant, which might be due to the use of a relatively small sample size. Furthermore, although naltrexone shows highest sensitivity for the mu-opioid system, we cannot disregard the possibility of effects via the kappa- or delta-opioid receptor systems. Finally, only females were included in the study due to the fact that females show more robust facial mimicry than males (Dimberg and Lundquist, 1990). To validate and extend the current results further testing is required, which should include a male sample.

In conclusion, we suggest that the mu-opioid system has a pivotal role in the underlying mechanisms that regulate the appetitive response to social reward cues, like happy faces. We show that naltrexone administration results in increases in negatively-valenced facial responses during the presentation of happy faces. This finding corresponds to the role of the mu-opioid system in social interaction and affiliation, and in adaptive socio-emotional behavior.

Chapter 4

Oxytocin increases reactivity in the amygdala and hippocampus to emotional stimuli of children in women depending on childhood emotional neglect

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In preparation

Abstract

Sensitivity for rewarding cues from- and empathic responses to the needs of children, are fundamental to human caregiving, and modulated by oxytocin (OXT). Here, in a functional magnetic resonance imaging (fMRI) study we investigate the effect of a placebo controlled, within-subject intranasal OXT (24 IU) administration in 24 healthy female subjects. In these women, we measured the effect of OXT on neural markers of reward sensitivity and affective empathy toward children in a newly developed neuroimaging task, using images of children in socially rewarding and distressing situations, compared to neutral. The task elicited valence specific effects, with positive images activating the ventromedial prefrontal cortex (vmPFC), bilateral precuneus, left anterior cingulate cortex (ACC), left anterior insula (AI) and right putamen, areas involved in emotion regulation and salience processing. Images of children in distress elicited activation in areas of emotion processing and affective empathy, including the bilateral amygdala, hippocampus, left thalamus and right medial superior frontal cortex. A main interaction effect of OXT administration on neural activity was only observed in the superior prefrontal cortex (sPFC). Nonetheless, exploratory analyses showed that subjective reports of emotional neglect interacted with OXT administration in the amygdala and hippocampus, and prefrontal areas. In individuals who reported to have experienced emotional neglect during childhood, OXT increased neural reactivity of amygdala and hippocampus to positive and neutral images to the level of individuals who experienced no or little emotional neglect. At the same time, a reduction of neural activity was observed in the PFC which suggests a change in prefrontal regulatory control, although this needs to be tested in future research.

Introduction

Two important components of human parental caregiving are sensitivity to rewarding signals from children and empathic responses to needs of children. A key modulator of sensitivity for social reward and empathy is the neuromodulatory peptide oxytocin (OXT) (Bethlehem et al., 2014; Bos et al., 2012). It is hypothesized that OXT increases the sensitivity to rewarding infant stimuli such as infant laughter (Riem et al., 2012) and simultaneously increases the empathic response to cues of distress such as infant crying (Riem et al., 2011). Empathy refers to the ability to automatically read, understand and react to feelings and intentions of others based on their bodily signals and is an important component of human social functioning. It contributes to communication, and to the formation and maintenance of social relationships, including the parent-infant bond (Bos, 2017; Decety, 2011; Feldman, 2017).

Empathy is however a multifaceted construct, composed of a cognitive aspect, contributing to the understanding of another person's perspective and actions, and an affective aspect which is expressed in the shared experience of affect. In addition, there is empathic concern which is defined by feelings of compassion and sympathy, and a clear distinction of self and other. The neuroendocrine effects of OXT vary depending on the different aspects of empathy. OXT seems to facilitate certain aspects of cognitive empathy, including emotion recognition (Bartz et al., 2010) and the processing of social cues (Domes et al., 2010; Hurlemann et al., 2010), however the effects of OXT on theory of mind and affective empathy are less straightforward (Leppanen et al., 2017). Under specific circumstances and on a subjective level, OXT has shown to increase empathy for pain, an evolutionary conserved aspect of affective empathy (Abu-Akel et al., 2015; Shamay-Tsoory et al., 2013). The neural activation related to seeing others in physical pain, however, has been shown to be reduced after administration of OXT, in line with its pain reducing properties (Bos et al., 2015). Due to the high aversiveness of the physical pain stimuli used in the study (videos of a needle being inserted into a hand) it is possible that the effects of OXT were driven by a reduction of personal distress, an adaptive response to facilitate attention relocation and a shift towards helping behavior.

Therefore, in the current study, which was part of a larger project investigating the hormonal precursors of parental caregiving (Bos et al., 2018), we developed a new neuroimaging paradigm to investigate the effect of OXT on sensitivity for social reward and affective empathy towards children. The stimuli showed children depicted in situations of distress and positive social interactions, compared to children in neutral situations. Based on independent subjective evaluations, stimuli of children in emotional distress were selected to elicit sympathetic, but not aversive responses which might occur during the observation of physical pain in others. Because of OXT's crucial role in caregiving behavior (Bos, 2017; Feldman, 2017), empathic as well as rewarding responses to children should especially be driven by OXT, hence our selection of emotional stimuli depicting children in different affective scenarios.

It has become apparent though, that the effects of OXT do not only vary depending on task selection, but are also strongly determined by context and individual characteristics (Bartz et al., 2011; Olff et al., 2013; Shamay-Tsoory and Abu-Akel, 2016). Exposure to childhood adversity is one such characteristic that could affect OXT function. Childhood adverse events can comprise neglect and abuse on an emotional and physical level, as well as chronic exposure to stress. Especially adverse events during early childhood can result in long-lasting changes in neural, endocrinological and social functioning (Bos, 2017; Lanius et al., 2010), and hence increase vulnerability to stress and disease (Heim et al., 2008), and negatively affect parenting behavior (Bos, 2017). Part of these effects could be mediated by alternation in functioning of the OXT system.

Indeed, early life adversities (ELA) were found to be associated with decreased OXT cerebrospinal fluid (CSF) concentrations in women and non-human primates (Heim et al., 2009; Strathearn, 2011) and with decreased OXT plasma levels in men (Opacka-Juffry and Mohiyeddini, 2012). Children who experienced severe emotional neglect early on, showed no change in OXT levels after physical contact with their mother, whereas children who were raised in a caring environment showed an increase of OXT (Fries et al., 2005). Neural responses to OXT administration also seem to be dependent, and can even be dissociated, depending on ELA, which has repeatedly been shown in male participants in studies relating to stress reactivity (Fan et al., 2015; Grimm et al., 2014; Meinlschmidt and Heim, 2007). In a stress related task, subjects with history of ELA showed enhanced task related effects in limbic structures after OXT administration, whereas controls showed a reduction (Grimm et al., 2014). Another paper, in the same sample, showed that the degree of ELA was positively related to amygdala-hippocampal functional connectivity during the stress task which then was attenuated by oxytocin (Fan et al., 2015). Moreover, a study investigating resting state connectivity in women found OXT to induce changes in functional connectivity in the default mode network, which were absent in individuals who experienced maternal love withdrawal as a disciplinary action (Riem et al., 2013). Besides these studies, the significance of ELA on OXT effects in neural responses related to caregiving motivation have not been studied extensively.

In addition to early childhood adversities, OXT effects have been shown to be sex-dependent, for example amygdala reactivity to fearful faces after OXT was found to be enhanced in women, but decreased in men (Domes et al., 2010; Lieberz et al., 2019). Therefore, in the current study we critically address the effects of OXT on the empathic neural response to children in a functional neuroimaging setup in women only (N=26). OXT (24 IU) was administered intranasally in a placebo controlled, randomized within-subject design. In an additional task post-scanning, participants were asked to give a subjective empathy rating of the images they had seen in the scanner. In line with the social salience theory of oxytocin (Bartz et al., 2011; Bethlehem et al., 2014; Shamay-Tsoory and Abu-Akel, 2016) it can be hypothesized that OXT will increase the neural response to images with children in positive social interactions in structures related to

reward, salience and cognitive empathy, including the nucleus accumbens (Nacc), ventromedial prefrontal cortex (vmPFC), ventral tegmental area (VTA), putamen, caudate nucleus and thalamus. However, recent work from our own lab in this same sample of women, showed reduced activation in neural responses toward infant faces after OXT in areas related to reward and salience, and this effect was modulated by caregiving motivation (Bos et al., 2018). It can therefore also be expected that similar responses will be observed towards the positively-valenced stimuli. For images depicting children in emotional distress, in line with previous literature of the effects of OXT on emotional reactivity in women (Lieberz et al., 2019), we expect OXT to increase neural reactivity in structures involved in emotion processing, including the amygdala, hippocampus, anterior insula (AI), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC). Further, we expect that these OXT effects depend on inter-individual differences in history of childhood emotional neglect and caregiving motivation, considering OXT's crucial role in caregiving behavior and our recent findings of OXT effects toward infant stimuli being modulated by caregiving motivation (Bos et al., 2018).

Material and Methods

Participants

A group of twenty-six healthy, female participants were recruited at Utrecht University campus to take part in the study. To avoid hormonal fluctuations during the cycle only women using combined oral contraceptives (OCs; i.e. containing ethinylestradiol and levenorgestrel; Microgynon 30) were included in the study, and no scans were performed the hormone-free interval of the OC regimen (Montoya and Bos, 2017). Participants had no history of psychiatric, neurological, or endocrine abnormalities. Participants did not smoke and used no medication other than OCs. Participants were informed not to consume alcohol or other drugs 24h, and not to eat or drink 1h prior to testing sessions. With regard to drug administration (nasal spray), testing sessions were rescheduled when participants experienced a blocked or running nose.

The experimental protocol was approved by the ethics committee of the University Medical Centre Utrecht, in accordance with the latest declaration of Helsinki. All participants gave written informed consent prior to participation in the study and received payment afterwards. Due to technical issues during fMRI acquisition (artifacts, n = 4) the final sample consisted of 22 participants (mean age M = 20.25; sd. = 1.33; range = 18-24).

Drug administration

The setup of the study followed a within-subjects, double-blind, placebo-controlled, counterbalanced crossover design in which 24 IU of OXT was administered (Syntocinon nasal spray; Defiante Farmacêutica, S.A.). Participants self-administered 3 puffs (8 IU per puff) per nostril under supervision of the experiment leader. The placebo consisted of a NaCl solution produced by the pharmacist of the University Medical Centre Utrecht in accordance with GCP guidelines.

Procedure

Participants were scanned on two separate days, always at the same time of day in a time frame between 12:00 and 17:00 hours, with a minimum interval of 72h between sessions. Before drug administration participants were screened for alcohol and drug use, were given brief explanation of the task and gave written informed consent.

Participants self-administered the nasal spray under supervision of the experiment leader and were seated in a waiting room until asked to proceed to the scanner. Before entering the scanner, participants were screened using an MRI checklist and a metal detector, and subsequently were instructed to position themselves on the scanner bed as comfortable as possible and try to relax. Foam pads placed between the radiofrequency (RF)-coil and the participant's head were used to minimize head movement. Instructions and task images were displayed on an MRI-compatible monitor placed at the head-end of the scanner visible via an angled mirror attached to the coil. Further communication between participant and experiment leader during the scan session was done via intercom. Average time interval between OXT administration and the start of the task was 59 Min (sd. = 5.47), which is in line with most studies showing effects of OXT on behavior so far (Bos et al., 2012). At the end of the second session participants were asked to guess on which day they received OXT. They were not aware which day they received OXT or placebo (binomial: $p > .05$). Last, all participants were debriefed and received payment. To control for mood effects of OXT the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) was filled out twice, once before administration upon arrival in the laboratory and once directly before proceeding to the scanner (~30min after administration).

After the second day of testing, participants were emailed with the request to fill out a Dutch online version of the Childhood Trauma Questionnaire – Short Form (CTQ) (Thombs et al., 2009) and PCAT questionnaire (Buckels et al., 2015). The CTQ measures childhood maltreatment on 5 separate constructs, namely emotional and physical neglect, and emotional, physical and sexual abuse (Bernstein et al., 2003). The subscale that we considered for the current study, emotional neglect (CTQ-EN), is based on the definition of "the failure of caretakers to meet children's basic emotional and psychological needs, including love, belonging, nurturance, and support." (Bernstein et al., 2003). We chose this subscale of the CTQ based on the findings of a previous administration study in relation to infant stimuli (Bos et al., 2014). Mean score of our sample on the CTQ-EN was 8.1 (sd., 2.65; range, 5-15) which is comparable with scores obtained in the non-clinical sample of the Dutch validation study (Thombs et al., 2009). Cronbach's α for the CTQ-EN in the Dutch validation study was 0.91 including clinical and non-clinical samples (Thombs et al., 2009).

The PCAT measures parental care motivation (Buckels et al., 2015) that consists of the conceptually separate constructs nurturance and protection, where the former uniquely predicts sensitivity for infant cuteness, whereas the latter predicts restrictive parenting practices and harsh moral judgments on moral transgressions (Hofer et al., 2017). In the validation study

Cronbach's α of the PCAT-n was 0.88 (Hofer et al., 2017) and for the current sample we obtained a Cronbach's α of 0.75. Mean score on the PCAT-n was 3.7 (sd., 0.76; range, 1.83–4.83).

Children empathy task and behavioral ratings

The empathy task, a passive viewing task, was designed to measures empathic responses to positive and negative scenarios. Participants were presented with different black-and-white stimuli depicting children in scenes with an emotionally negative, positive or neutral context. Positive stimuli showed rewarding social interactions, children playing together or parent infant interactions. Negative images showed children in distressing scenes, for example an isolated crying child. Based on independent subjective evaluations, stimuli were selected that elicit sympathetic, but not aversive responses, therefore limiting the possibility of personal distress in our participants, which might occur during the observation of physical pain in others. Neutral images depicted children executing a task or playing with toys, with a neutral facial expression and without social interaction. Stimuli were pre-selected through a rating procedure from a larger set of 120 images obtained after an internet search in a pilot study. Images were rated on empathic content and positivity by 24 female participants (mean age M = 34.45, sd. = 15.03) and in total ten stimuli were selected per condition based on consistency of the ratings. The resulting conditions vary significantly on empathic content ($F(2,46) = 450.70$, $p < .001$, $\eta 2 = .95$) and positivity ($F(2, 46) = 318.98$, $p < .001$, $\eta 2 = .93$).

A total of 72 images, 24 images per condition, were presented to the participant in a block design, with each image being presented twice but randomized and never within the same block. This resulted in a total of 18 blocks, divided into 6 blocks per condition. Every block lasted 24000ms and consisted of 8 stimuli of the same valence, each presented for 3000 ms. A fixation cross was displayed at the start of the task and at the beginning of each block for the duration of 5500 ms.

Participants were instructed to attend the images presented to them carefully, and to imagine themselves in the situation that the child is pictured in. The same task was performed in both sessions. At the end of each fMRI session, outside of the scanner, participants performed an additional rating task containing a random selection of 36 pictures from the same stimuli, 12 of each condition, on how much compassion ('medelijden') the felt for the child in the image on a 10-point Likert scale (0 = No feeling of compassion; 9 = Very strong feeling of compassion). Participants never rated the same stimulus twice during the two sessions. The rating scores were used to perform an exploratory behavioral analysis.

Scanning parameters

Scanning was performed on a 3 Tesla Philips Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands). Before the functional scans, a high resolution anatomical T1-weighted scan with the following parameters was obtained for co-registration and normalization purpos-

es: 3.8 ms echo time, 8.4 ms repetition time, 288x288x175 mm field of view, 175 sagittal slices, flip angle of 8.0°, voxelsize 1.0 mm isotropic.

Blood oxygen level dependent (BOLD-) response was measured with functional T2*-weighted axial whole-brain images. In each session 490 volumes were acquired during the task using a 2D-EPI-SENSE sequence with 51 slices, a flip angle of 65°, voxel size of 2.5mm isotropic, a SENSE-factor of R= 3.0 (anterior-posterior) and a field of view of 220x127.5x220 mm. Repetition time (TR) for volume acquisition was set to 1.01s and the echo time (TE) to 24 ms.

Preprocessing and data analyses

Preprocessing and subsequent analyses were performed with SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Functional scans of both sessions were motion corrected after which the anatomical scan was then coregistered to the mean functional scan. Subsequently, using unified segmentation, the structural scan was segmented and normalization parameters were estimated. Using these normalization parameters, all volumes were normalized to a standard brain template (MNI) and were resliced at 2 mm isotropic voxel size. Smoothing with a 6 mm full width at half maximum Gaussian kernel was ap- plied to the normalized functional volumes. Next, within both sessions, a general linear model (GLM) was applied to the data to investigate the effects of stimulus conditions. Neural responses to the different conditions of emotional valence were modeled using a 24 s boxcar function convolved with a hemodynamic response function (hrf) as implemented in the SPM12 software. Additional regressors of no interest which are entered into the analyses to reduce unexplained variance in the data include realignment parameters and a discrete cosine transform high-pass filter with a cutoff of 128 s.

Next, contrast maps for the different emotional valence conditions vs baseline of both sessions were entered into a second-level factorial ANOVA, with drug (OXT vs placebo) and emotional valence (negative, neutral and positive) as within-subject factors. F-tests were run to test for the effect of condition (emotional valence), drug and for the interaction effect of OXT with condition. To examine the (de)activations of all stimuli vs rest comparative t-tests were performed. Further, to test for emotion specific effects comparative t-tests were performed for the contrasts negative > neutral and positive > neutral, with the data from both sessions (OXT and placebo) combined.

To control for multiple comparisons in the whole-brain analyses a threshold was set at $P < 0.05$ (family-wise error (FWE) corrected). Additionally, small volume corrections (SVC; $p < 0.05$ FWE) were applied for the predefined regions of the interest (ROIs): the amygdala, hippocampus, AI, ACC, OFC, putamen, caudate nucleus and thalamus were based on the automated anatomical labeling (AAL) template (Tzourio-Mazoyer et al., 2002). The VTA, the Nacc and the vmPFC are not included in the AAL atlas as masks and were therefore computed based on previous empirical papers and a meta-analysis. The mask for the VTA

was based on (Groppe et al., 2013) and consists of 2 spheres of 10 mm radius around MNI coordinates ±9, −18 and −18. The bilateral mask for the Nacc was retrieved from (Montoya et al., 2014). The mask for the vmPFC is based on a meta-analysis on theory of mind by Bzdok et al., (2012) built with a 10mm sphere around the MNI coordinates 0, 52 and -12. For all predefined anatomical ROIs that showed significant effects in the emotion specific t-contrasts (negative > neutral; positive > neutral) on whole brain level, percentage signal change was extracted using MarsBaR (Brett, 2002) for further exploratory analyses.

To investigate the effect of the CTQ-EN and PCAT-n on the neural responses towards images of different emotional valences as well as the interaction of CTQ-EN and PCAT-n with OXT administration exploratory analyses were conducted. The extracted values of each ROI were entered into a separate 2x3 ANOVA with drug (OXT and placebo) and condition (negative, neutral and positive) as within-subject factors and the respective questionnaire as a covariate. Subsequently, CTQ-EN scores and PCAT-n scores were correlated with the extracted ROI parameters to describe the interaction effects.

Behavioral rating data was first screened for outliers, defined as scores higher than 3 sd. above the mean score, in each condition separately. Based on this criterium all 22 participants were included in the analysis. Next, scores were averaged over trials by condition (negative, neutral and positive) and drug (OXT vs. placebo), tested for normality with a Shapiro-Wilk test and then entered in a 2 (drug) x 3 (emotional valence) non-parametric analysis of variance (Friedman test). SPSS 23 (IBM analytics) was used for statistical analysis of the behavioral data and a α of 0.05 was applied to test for significance.

Results

Behavioral data

A 2 (OXT vs placebo) x 3 (negative, neutral, positive) Friedman's ANOVA revealed a statistically significant difference between empathy ratings, depending on image valence and drug ($\chi 2(5) = 93.33$, $p < .0001$). Post-hoc analyses were conducted using Wilcoxon signed rank tests with Bonferroni correction applied, with the statistical significance level set at $p < .009$. To test for task effects, pairwise comparisons in the data from both sessions (OXT and placebo) combined showed that all conditions differed significantly from each other on ratings of compassion (neg vs neut: Z = -4.1, $p < .001$; pos vs neut: Z = -4.1, $p < .001$; neg vs pos: Z = -4.1, $p < .001$). Negative images (M = 7.56, sd. = .79) were rated significantly higher on compassion than positive (M = .36, sd. = .38) and neutral ones (M = 1.13, sd. = .83), and neutral images higher than positive ones. To test for OXT administration effects on ratings, pairwise comparisons showed a marginally significant effect for ratings of neutral images (Z = -2.32, $p = .02$) which did not survive the threshold of .009, with lower ratings after OXT (M = 1.003, sd. = .90) compared to placebo (M = 1.25, sd. = .88). All other p-values were $p > .30$.

Mood data

To test for possible effects of OXT on mood within and between the two testing sessions, the sum scores on the positive and negative affect scale of the PANAS (Watson et al., 1988) were entered into a 2 x 2 repeated measures ANOVA with drug (OXT, placebo) and time of measurement (before and after drug administration) as within subject factors. OXT did not affect mood ratings on the positive ($F(1,21) = .001$, $p = .974$, $\eta 2 = .00$) and negative ($F(1,21) = .011$, $p = .918$, $\eta 2 = .001$) scale, nor did it interact with the time of mood measurement for positive ($F(1,21) = .981$, $p = .333$, $\eta 2 = .05$) or negative ($F(1,21) = 3.36$, $p = .081$, $\eta 2 = .14$) affect scores. Overall mean scores on the PANAS were M = 34.4 (sd. = 4.9) for the positive affect scale and M = 12.8 (sd. = 2.8) for the negative affect scale.

Functional neuroimaging data

In the full factorial analysis on whole brain level, the F-test for main effect of condition resulted in extensive activation including bilateral visual cortices, fusiform gyrus, inferior parietal- and temporal gyri, the precuneus and the medial superior frontal cortex, including the following of our ROIs: hippocampus, amygdala, insula, ACC, vmPFC and thalamus (see Table 1, supplementary materials). VTA, Nacc, putamen and caudate nucleus showed no significant activation on whole brain or ROI level.

Across both drug conditions, t-tests for the specific effect of positive > neutral (Fig. 1A, Table 1) showed significant activation in occipital areas ($p < .01$), the left vmPFC ($p < .05$) and the bilateral precuneus ($p < .05$). Further analyses within our a priori ROIs resulted in significant activation of left ACC ($p < .01$, SVC), left anterior insula ($p < .01$, SVC) and right putamen ($p < .001$, SVC). The t-test for negative > neutral (Fig. 1B, Table 1) resulted in significant activation of the bilateral hippocampus ($p < .05$) and the right medial superior frontal cortex ($p < .05$). In addition, significant activation was found in the bilateral amygdala ($p < .001$, SVC) and the left thalamus ($p < .001$, SVC).

We found a significant interaction of drug*condition on whole brain level in the superior prefrontal cortex (sPFC; -22 56 6; $p < .05$, FWE; Fig. 1C and Table 1) only. A repeated measures ANOVA on the extracted values of that functional ROI, resulted in a significant interaction of drug*condition ($F(2,42) = 12.24$, $p < .0001$, $\eta 2 = .37$) confirming the result found on whole brain level, and indicating a decrease of activation after OXT in the positive (OXT: M = -.208, sd. = .048; placebo: M = -.034, sd. = .031) and neutral condition (OXT: M = -.136, sd. = .041; placebo: M = -.07, sd. = .04) and an increase in the negative condition (OXT: M = -.135, sd. = .039; placebo: M = -.183, sd. = .037). Post-hoc paired sample t-tests on the extracted values of the sPFC ROI showed a significant decrease of activation in the positive condition ($t(21) = -3.46$, $p = .002$), but no significant change in the negative or neutral condition ($p = .39$ and $p = .23$ respectively). No interaction effects were found in the a priori ROIs (p's > .05) and no overall main effect of OXT was found on whole brain level and in any ROI.

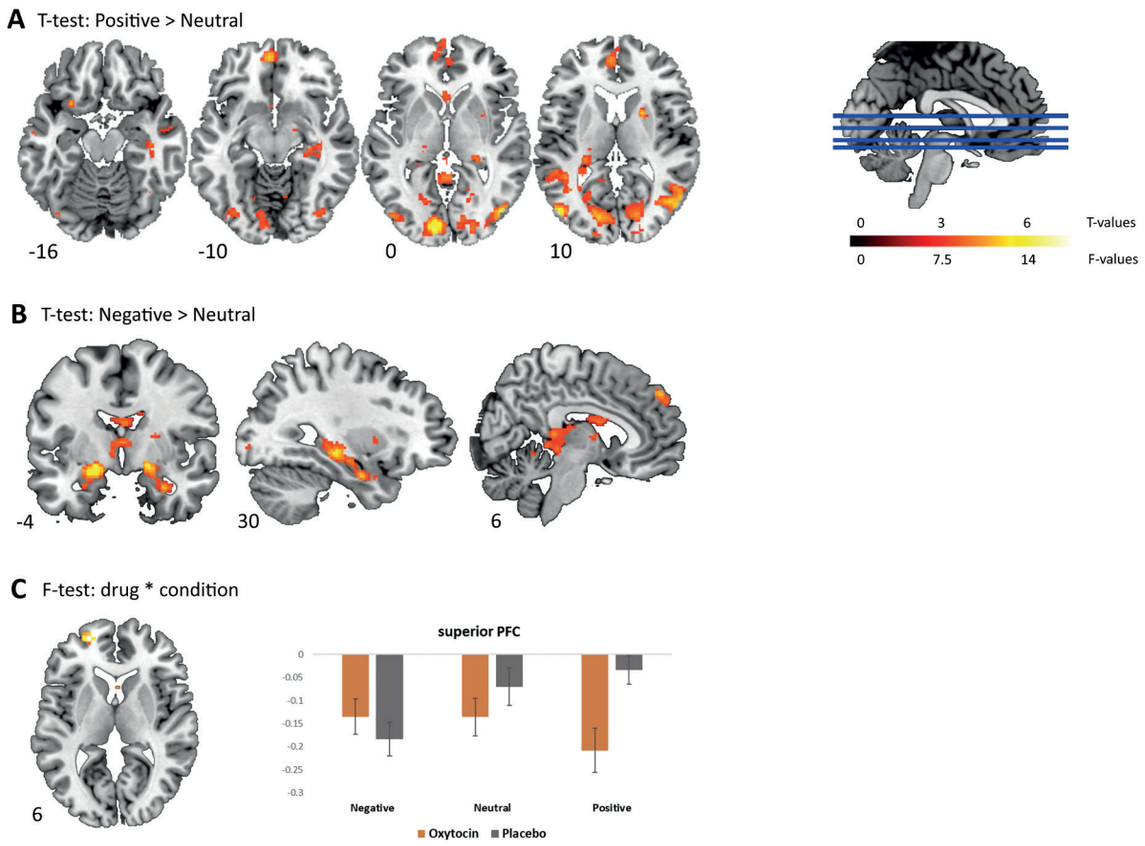

Fig 1. A, Axial slices with corresponding Z-coordinates (MNI) from the T-map of neural activation for positive vs. neutral images, depicting significant activation in the left anterior insula, left vmPFC, left ACC and right putamen, overlaid onto a standard anatomical template. B, One coronal and two sagittal slices with corresponding X- and Y-coordinates (MNI), respectively, from the T-map of neural activation for negative vs. neutral images. Significant activation of bilateral amygdala, bilateral hippocampus, left thalamus and right medial superior frontal cortex are depicted. C, Axial slice with corresponding Z-coordinate (MNI) from the F-map of neural activation for the interaction of drug*condition, depicting significant activation in the left superior PFC. A bar graph of the parameter estimates, extracted from a 10mm sphere around the functional ROI of the left superior PFC, in all conditions vs. rest is displayed. Accompanying statistics are described in the text. All statistical maps are thresholded at P = .001 uncorrected, for illustration purposes only.

To investigate the effect of individual differences of having experienced childhood emotional neglect, we conducted additional exploratory analyses adding the CTQ-EN scores as a covariate in separate repeated measures ANOVAs with the extracted values of a priori ROIs that were found to be significant in the emotion specific t-tests (positive > neutral; negative > neutral), and the extracted values from the sPFC. The CTQ-EN significantly interacted with OXT administration in the amygdala ($F(1,20) = 6.12$, $p = .022$, $\eta 2 = .24$) and with OXT*emotional valence in the hippocampus ($F(2,40) = 3.67$, $p = .034$, $\eta 2 = .155$) and the putamen ($F(2,40) = 3.86$, $p = .029$, $\eta 2 = .162$). In the prefrontal regions CTQ-EN significantly interacted with OXT

administration in the extracted values of the functional ROI in the sPFC ($F(1,20) = 64.3$, $p = .051$, $\eta 2 = .18$) and with OXT*emotional valence in the vmPFC ($F(2,40) = 5.32$, $p = .009$, $\eta 2 = .21$) and the ACC ($F(2,40) = 3.43$, $p = .042$, $\eta 2 = .147$).

Subsequently, to test for the direction of these effects, the CTQ-EN was added in a correlational analysis with the extracted values of the a priori ROIs amygdala, hippocampus, vmPFC, ACC and the extracted values of the sPFC. We found significant negative correlations between childhood emotional neglect and activation in the amygdala after placebo in all three conditions (positive conditions: r = -.618, $p = .002$; neutral condition r = -.457, $p = .033$, see Fig. 2A and B; albeit marginally significant in the negative condition: r = -.412, $p = .056$), whereas no such relations were observed in the OXT conditions (positive: r = -.091, $p = .687$; neutral: r = -.206, $p = .358$; negative: r = -.082, $p = .716$). Similarly, a negative correlation between CTQ-EN and activation in the hippocampus was found for positive images only after placebo (r = -.641, $p = .001$), but not after OXT (r = -.128, $p = .570$; Fig. 2C).
At the same time, negative correlations between childhood emotional neglect and activation in prefrontal ROI's was found in the OXT condition which did not hold for placebo (Fig 2D and E). We found a negative correlation of CTQ-EN with activation in the vmPFC after OXT for the neutral condition (r = -.539, $p = .01$; not for placebo: ; r = -.01, $p = .964$; Fig 2D) and for the sPFC after OXT for the neutral condition (r = -.492, $p = .02$; r = .126, $p = .576$ Fig 2E).
No significant correlation was found between CTQ-EN and ACC, or CTQ-EN and putamen (all $p < .05$). Hence, emotional childhood neglect was negatively associated with neural activation in amygdala and hippocampus under placebo, whereas this association disappeared under OXT. At the same time, activation in the frontal regions, sPFC and vmPFC, were negatively associated with childhood emotional neglect under OXT exclusively.

Next, to test whether caregiving motivation was a predictor of OXT effects on neural activity, we conducted exploratory analyses in the same manner, adding the PCAT-n scores as a covariate in the separate repeated measures ANOVAs with the extracted values of ROIs that were found to be significant in the emotion specific t-tests (positive > neutral; negative > neutral), and), and the functional ROI extracted from the sPFC. The PCAT-n significantly interacted with OXT administration in the putamen ($F(1,20) = 4.99$, $p = .037$, $\eta 2 = .20$), but not in any of the selected ROI's (all $p > .05$). To test for the direction of this effect, the PCAT-n was added in a correlational analysis with the extracted values of the putamen ROI. A significant negative correlation was found between PCAT-n and activation of the putamen for neutral images after placebo (r = -.452, $p = .035$), but not after OXT (r = .276, $p = .214$). The correlations for positive (placebo: r = .-147, $p = .515$; OXT: r = .200, $p = .373$) and negative images (placebo: r = .-221, $p = .323$; OXT: r = .266, $p = .231$) were in the same direction, but not significant.

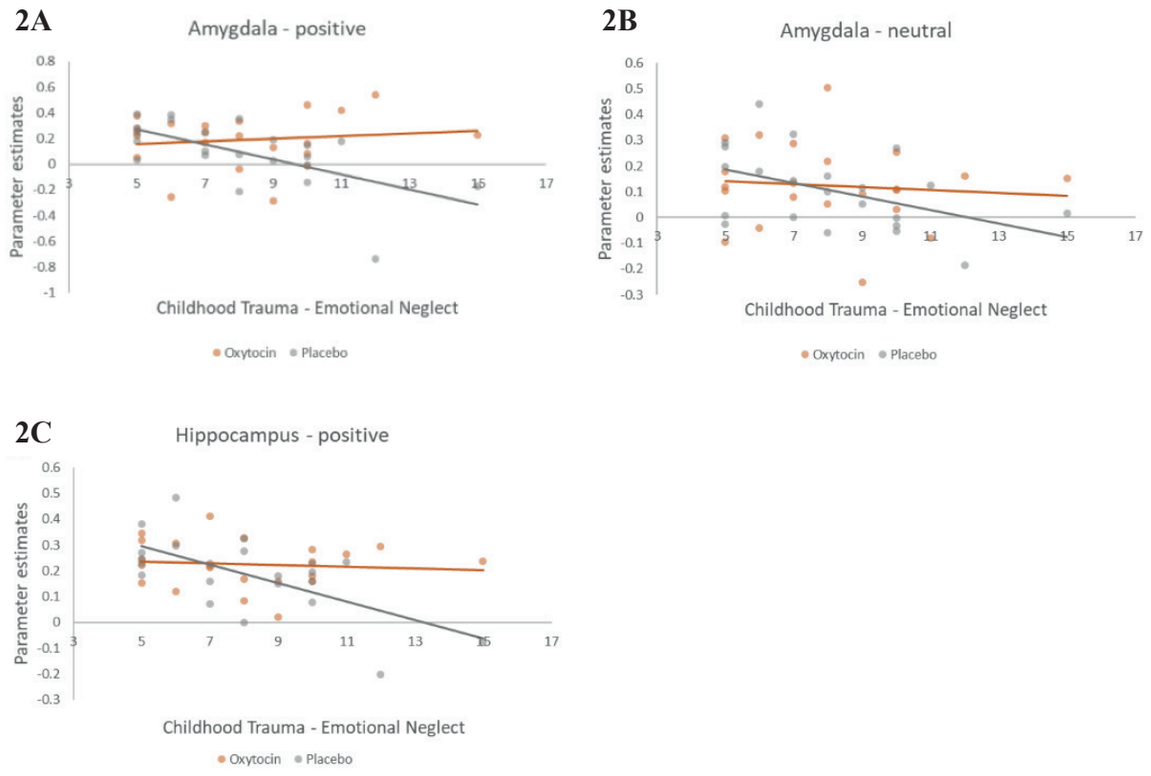

Fig 2. A&B, Scatterplots of the correlations between extracted parameter estimates from the anatomical bilateral amygdala toward positive (A) and neutral (B) stimuli, and the participant scores of the CTQ-EN, for OXT and placebo.
C, Scatterplot of the correlation between extracted parameter estimates from the anatomical bilateral hippocampus toward positive stimuli and the participant scores of the CTQ-EN, for OXT and placebo. Accompanying statistics are described in the text.

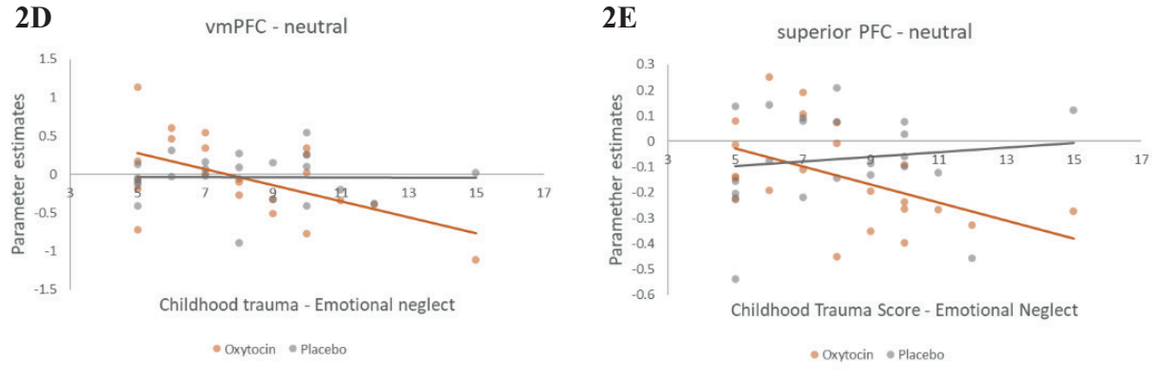

Fig 2. D, Scatterplot of the correlation between extracted parameter estimates of a 10mm sphere around the MNI coordinates 0 52 -12 (Bzdok et al., 2012) toward neutral stimuli and the participant scores of the CTQ-EN, for OXT and placebo.
E, Scatterplot of the correlation between extracted parameter estimates from the functional ROI of the sPFC (cortex (-22 56 6) toward neutral stimuli, and the participant scores of the CTQ-EN, for OXT and placebo. Accompanying statistics are described in the text.

Discussion

In this study we investigated the effects of OXT on neural responses of social reward and affective empathy towards images of children in a newly developed neuroimaging task, in healthy nulliparous women. As expected, the task evoked emotion specific effects with respect to neural responses and subjective ratings. The ratings on how much compassion participants felt with the children depicted in the images, validated our task on a subjective level, with negative images receiving significantly higher ratings of compassion than neutral or positive ones. Neutral images were rated significantly higher in compassion than positive images, possibly due to higher ambiguity of the stimuli, displaying no clear negative or positive situation. Testing for the effect of OXT administration on subjective feelings of compassion toward the children in the images showed no significant results after correction for multiple comparisons.

On the brain level, images depicting socially rewarding interactions between children activated areas related to reward and salience processing (Bos et al., 2015; Seeley et al., 2007), including the vmPFC, precuneus, ACC, anterior insula and putamen. There was however no significant activation of Nacc, caudate and VTA, core structures involved in the processing of reward (Haber and Knutson, 2010; Peciña et al., 2006). At the same time, images depicting children in distress elicited activation in the hippocampus, amygdala, thalamus and medial superior prefrontal cortex, areas related to emotion processing and affective empathy (Decety, 2011; Reniers et al., 2014), validating our paradigm as an adequate tool to investigate the neural foundation of affective responses to children. We did not observe effects of OXT in any areas that showed task related effects, but an interaction effect of OXT and emotional valence was found in the left sPFC. OXT induced a significant decrease of activation to positive stimuli in the sPFC. This finding should be interpreted with caution given that the region did not show task-related effects and did not belong to our a priori ROI's. Previous research found the left sPFC to be mainly involved in working memory load (Boisgueheneuc et al., 2006).

We found task related activation of the ACC, AI, vmPFC and putamen toward images of socially rewarding interactions in children, which are areas involved in salience processing, reward and theory of mind (Bzdok et al., 2012; Haber and Knutson, 2010; Seeley et al., 2007). That these areas were responsive without co-activation of Nacc, caudate and VTA, was unexpected. In our previous work on the same sample of women we did show activation in the bilateral VTA as well as putamen, amygdala, insula and ACC in response to infant faces (Bos et al., 2018), therefore stimulus differences might have played a role. Indeed, previous literature shows variation in activation of the reward system towards social stimuli depending on sex-, task- and stimulus related differences (Gregory et al., 2015; Groppe et al., 2013; Spreckelmeyer et al., 2009). For example, a study investigating the neural response to infant laughter, another reward signal related to caregiving, in nulliparous women showed activation of prefrontal areas, brainstem, amygdala and putamen, but no response in the Nacc (Riem et al., 2012). Especially the lack of VTA activation in our study might be due to our paradigm being a passive viewing task

within a block design, whereas VTA activation is often related to anticipatory and motivational components of reward in performance tasks (Spreckelmeyer et al., 2009).

Regarding the neural activation in response to images of children in distress, our current study showed strong activation of the amygdala, hippocampus, thalamus and prefrontal areas. Sensitivity of these regions to distress is highly relevant for caregiving behavior as it reflects increased emotion processing and empathy (Bos et al., 2014; Feldman, 2017). We did not find significant activation of the AI, ACC or sensorimotor cortices which were found to be activated in response to watching physical pain stimuli with a high aversive component (Bos et al., 2015). The insula might be more responsive to rather direct signals of children's distress, such as infant crying (Witteman et al., 2019).

Against our expectations no significant effect of OXT administration on neural activity in any of the a priori ROIs was found. Based on previous findings in the same sample of women (Bos et al., 2018), we expected OXT to affect VTA activity in response to socially rewarding infant stimuli. However, OXT has formerly been found to differ in its effect on neural reward responses depending on the type of social reward stimuli. Indeed, OXT strongly increased neural activation in response to sexual reward stimuli, but not to positive infant stimuli, in both nulliparous and postpartum women (Gregory et al., 2015). Furthermore, contrary to studies that showed effects of OXT administration on neural activity to infant crying (Riem et al., 2011) or viewing physical pain stimuli (Bos et al., 2015), we found no effect of OXT administration to negative stimuli. The study investigating neural responses to infant crying found a deactivation of the amygdala but an increase in activity in the AI and inferior frontal gyrus after OXT (Riem et al., 2011), whereas OXT administration reduced the neural response in the insula, the medial cingulate cortex and the somatosensory cortices to stimuli picturing physical pain (Bos et al., 2015). The disparity of response patterns could be due to the difference in task stimuli and possibly to varying degrees of aversiveness. Finally, it should be taken into account that our sample consisted of OC users. In another study OC users showed suppressed OXT-induced reward responses to social reward in the ventral striatum and VTA, compared to naturally cycling women (Scheele et al., 2016). Therefore, OC use could have contributed to the fact that we did not find OXT effects on neural responses to images of socially rewarding interactions in children, in our study.

With respect to inter-individual characteristics, we hypothesized that the function of OXT modulation would vary with differences in caregiving motivation (Bos et al., 2018) and parental emotional neglect (Fan et al., 2015, 2014; Grimm et al., 2014; Meinlschmidt and Heim, 2007). For parental emotional neglect (EN), exploratory analyses showed differential effects of OXT within the amygdala, hippocampus and prefrontal regions in individuals who reported to have experienced high compared to low EN. More specifically, in high EN individuals OXT increased neural reactivity to positive and neutral stimuli in the amygdala, and to positive stimuli in the hippocampus. Moreover, in high EN participants OXT administration attenuated activa-

tion in the vmPFC and sPFC to neutral images, which could suggest a decrease in regulatory prefrontal control to stimuli of neutral content. Whether this decrease in activation allows for an increase of neural reactivity on the level of amygdala and hippocampus needs to be tested in future research, but existing literature indicates changes of connectivity between especially the amygdala and prefrontal areas in ELA (Fan et al., 2015, 2014; Frijling et al., 2016). We herewith show for the first time, to our knowledge, that OXT modulates activity in limbic and prefrontal structures to infant cues depending on childhood EN in women.

Our findings are difficult to directly compare with other studies that look at the interaction of OXT administration and ELA, since these measure stress reactivity or resting state (Fan et al., 2015, 2014) and are mostly conducted in male subjects where sex differences in OXT effects can be expected (cf. Lieberz et al., 2019). It is therefore of interest to consider studies with paradigms more similar to our own study design, which have been conducted in individuals with post-traumatic stress disorder (PTSD) and who experienced trauma during adulthood. Of course, PTSD and trauma exposure during adulthood are not directly comparable with ELA, especially considering our sample is sub-clinical, however the following studies seem relevant to the interpretation of our findings.

Research investigating neural reactivity to emotional stimuli in a mixed sex sample of adults shortly post-trauma showed increased right amygdala reactivity to negative emotional stimuli after OXT compared to placebo. In addition, women showed an increase of left amygdala activity to neutral stimuli after OXT (Frijling et al., 2015). Interestingly, another study found that OXT decreased amygdala reactivity to emotional stimuli independent of valence in a mixed sex sample of PTSD patients, but enhanced amygdala reactivity to all stimuli in matched healthy trauma exposed controls (Koch et al., 2016). The finding of increased emotional reactivity after OXT in the amygdala in healthy trauma exposed adults (Koch et al., 2016) is very much in line with our own findings. The difference in the effect of OXT administration on neural activity between the two populations could be mediated through changes in receptor expression in individuals with PTSD compared to more resilient controls, possibly indicating that trauma severity and resilience to stress might be decisive factors in changes of OXT sensitivity. Indeed, L. Nawijn et al. (2019) showed that increased OXT receptor methylation (increased methylation resulted in reduced receptor expression; Gouin et al., 2017) was related to higher reports of anhedonia and reduced amygdala reactivity to emotional faces in individuals with posttraumatic stress disorder (PTSD).

Overall the results suggest that in individuals who experienced EN, OXT might boost emotion and salience perception of positive and neutral images of children by increasing activity in amygdala and hippocampus and decreasing activity in the vmPFC and sPFC. The direction of the effect is in line with the significant reduction of activity in the sPFC to positive images on whole brain level, independent of EN. Whereas negative cues are already highly salient, as can be seen by strong activation of amygdala and hippocampus in the task related effects for nega-

tive images, for high EN individuals positive or neutral images might be less salient in comparison. Therefore, salience is increased by OXT. Being responsive to reward signals from children is highly relevant for communication and bonding, and therewith a crucial aspect of caregiving behavior (Bos, 2017; Feldman, 2017). The found effect could therefore very carefully be interpreted as a compensation mechanism which allows attention allocation toward affective cues in individuals who show a deficit, which is in line with other effects of OXT dependent on individual characteristics and the salience theory of OXT (Bartz et al., 2011, 2010; Shamay-Tsoory and Abu-Akel, 2016). OXT might facilitate this increase in salience to reward signals and general social information from children via a reduction of prefrontal control, therefore future research should investigate the effect of OXT on functional connectivity changes in response to rewarding compared to neutral stimuli in individuals with ELA.

When looking at the interaction of OXT administration with caregiving motivation, we found a significant negative correlation of PCAT-n with neural activity in the putamen for neutral images after placebo, which disappeared after OXT administration. This result was unexpected and is not in line with findings from a previous study in this sample of women (Bos et al., 2018), where an increase of activity in the putamen was found in individuals with high PCAT-n scores which was attenuated after OXT. A possible explanation for this could be the difference in stimuli between the previous study (infant faces) and the current study (children in context), and the potential relevance of these stimuli to different individuals. Whereas infant faces might be especially relevant to women with high care motivation and therefore elicit strong activation of the putamen under placebo (Bos et al., 2018), children in context with no specific emotional valence might be less salient under placebo, but become relatively more salient after OXT, especially in participants with high care-giving motivation (Bos, 2017).

In conclusion, the study validated our newly developed neuroimaging task on neural responses to infant cues of different emotional valence. Effects of OXT administration were only found in the sPFC, and were dependent on the level of self-reported childhood emotional neglect for our hypothesized regions amygdala, hippocampus and vmPFC, and the level of parental motivation for the putamen. This study is the first, to our knowledge, to report that exposure to emotional neglect during childhood in a sub-clinical range in women, resulted in increased neural reactivity of amygdala and hippocampus, and a deactivation of prefrontal areas after OXT. The results suggest that OXT facilitates the processing of positive and neutral pictures from infants which is highly relevant for caregiving behaviors. This implicates that already sub-clinical exposure to emotional neglect during childhood can evoke changes in sensitivity of the OXT system that influence the attention and processing resources toward affective cues from children. The findings contribute to literature suggesting a crucial role for OXT in increasing salience perception of social cues (Shamay-Tsoory and Abu-Akel, 2016), highlighting the importance of individual characteristics.

Supplementary material

Table 1.

Overview of the peak T- and F-values, p-values, cluster sizes and MNI coordinates for significantly activated voxels.

Experimental effect Region	Side	Peak Voxel Location X	 Y	 Z	F/T value	Cluster size	*p*-values
Full factorial							
F-test: Main eff. Condition							
Temporal Mid R	R	48	-68	8	35.34	302	<0.001*
Occipital Mid L	L	-46	-76	10	32.42	266	<0.001*
Fusiform Gyrus	L	-24	-52	-14	29.94	84	<0.001*
Precuneus L	L	-2	-58	44	28.70	316	<0.001*
Inferior Temporal Gyrus	L	-52	-56	-12	26.25	64	<0.001*
Fusiform Gyrus	R	28	-46	-14	23.27	28	<0.001*
Precuneus R	R	-16	-58	62	23.22	23	<0.001*
Hippocampus	L	-16	-6	-12	22.19	19	<0.001*
Inferior Parietal Lobe	L	-48	-34	44	21.51	79	<0.001*
Vermis 3		-2	-32	-4	20.96	15	<0.01*
Occipital Mid L	L	-10	-92	0	20.42	40	<0.01*
Lingual Gyrus	L	-16	-66	-6	20.21	7	<0.01*
Hippocampus	R	18	-6	-10	19.18	3	<0.01*
Inferior Frontal Gyrus	R	36	32	10	19.02	7	<0.01*
Fusiform Gyrus	L	-32	-32	-24	18.38	3	<0.05*
Precentral Gyrus	L	-50	4	34	17.76	4	<0.05*
Hippocampus	L	-30	-28	-8	17.36	1	<0.05*
Medial superior frontal gyrus	R	6	50	40	16.86	1	<0.05*
Occipital Mid L	L	-32	-70	22	16.70	3	<0.05*
Cuneus R	R	4	-74	26	16.43	2	<0.05*
Amygdala	L	-18	-4	-14	19.11	59	<0.01**
Amygdala	R	22	-6	-12	14.29	12	<0.01**
Parahippocampal gyrus	R	30	-4	-28	9.45	3	<0.05**
Insula	R	36	32	8	15.33	2	<0.01**
Insula	L	-26	14	-16	12.49	1	<0.05**
Anterior cingulate cortex	L	-4	50	10	11.06	1	<0.05**
ventromedial prefrontal cortex	L	-4	54	-10	14.86	54	<0.001**
Thalamus	L	-2	-14	0	12.79	5	<0.01**
Thalamus	R	0	-12	6	10.40	1	<0.05**
F-test: Interaction Drug x Condition							
Superior frontal cortex	L	-22	56	6	16.28	1	<0.05*
T-test: Pos > Neutral							
Occipital Mid	L	-10	-92	0	6.38	107	<0.001*
Occipital Mid	L	-48	-76	12	6.19	47	<0.001*
Occipital Mid	R	46	-76	2	6.10	26	<0.001*
Occipital Mid	R	40	-68	18	5.78	61	<0.01*
ventromedial prefrontal cortex	L	-4	54	-10	5.44	3	<0.05*
Precuneus cortex	L	0	-56	42	5.36	32	<0.05*
Precuneus cortex	R	6	-56	52	5.10	1	<0.05*
Anterior cingulate cortex	L	-4	50	10	6.64	16	<0.01**
Anterior insula	L	-26	14	-16	4.60	2	<0.01**
Putamen	R	22	6	10	4.96	14	<0.001**
Putamen	R	28	8	4	3.98	1	<0.05**

Putamen	R	30	6	2	3.91	1	<0.05**
T-test: Neg > Neutral							
Hippocampus	L	-16	-6	-14	6.56	38	<0.001*
Hippocampus	R	18	-6	-10	6.19	15	<0.001*
Vermis 3		0	-32	-2	6.13	17	<0.001*
Hippocampus	L	-30	-28	-8	5.86	11	<0.01*
Hippocampus	R	30	-24	-8	5.54	6	<0.01*
Hippocampus	R	24	-14	-12	5.22	4	<0.05*
Medial superior frontal gyrus	R	6	50	40	5.10	1	<0.05*
Hippocampus	R	32	-28	-10	5.09	1	<0.05*
Amygdala	L	-18	-4	-14	6.16	16	<0.001**
Amygdala	R	22	-6	-12	5.18	1	<0.001**

R, right; L, left; *whole brain FWE corrected at cluster level, **small volume FWE corrected at cluster level.

Chapter 5

Social touch increases dominant gaze in social confrontations

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Submitted

Abstract

Positive effects of touch have been shown on the psychological and physiological level, with touch for example protecting us against the negative consequences of stress. Social touch however also induces feelings of security and willingness to take risks, characteristics of socially dominant behavior. The current study (N=24, female) investigates the effect of social touch on speed of gaze-aversion from eye-contact, an implicit marker of dominance-submissive behavior. Using interactive eye-tracking we show that social touch slows down gaze-aversion from subliminally presented angry compared to happy eye-contact. Recently, we reported slower gaze-aversion from subliminally presented facial anger in subjects with high levels of social dominance and low levels of social anxiety. The present results thus provide evidence that social touch induces gaze behaviors characteristic for high social dominance and low social anxiety. By slowing down gaze-aversion to facial anger social touch promotes the implicit-reactive behavioral tendency to engage in social confrontation.

Introduction

Social touch is crucial in our day-to-day lives. It is used to communicate emotions, contributes to resilience resources, and creates and strengthens social bonds (Burleson and Davis, 2014; Dunbar, 2010; Morrison et al., 2010). Social touch protects from and speeds up recovery after stress which is argued to provide for a sense of social security in humans (Jakubiak and Feeney, 2016a&b) and other primates (Dunbar, 2010). Indeed, social touch attenuated attentional bias to social threat in children (Brummelman et al., 2018), and initiated processes of emotion regulation resulting in a reduction of threat-related brain activity (Coan et al., 2006). Psychologically, even imagined social touch interactions increase the likelihood to engage more confidently in a social confrontation and promote exploration (Jakubiak and Feeney, 2016a). Interesting in this respect is that social touch acts on the core of our stress-system, decreasing heart-rate and cortisol responses to social stress in humans (Ditzen et al., 2007; Morrison, 2016), and inducing endorphin release in primates (Dunbar, 2010). These physiological findings suggest that social touch has the potential to not only promote social confrontation through psychological mechanisms (Jakubiak and Feeney, 2016a), but will do so implicitly by affecting automatic behavioral tendencies. Here, we therefore hypothesize that social touch will promote the implicit behavioral tendency to engage in social confrontation.

Behavioral mechanisms of dominance and submission are crucial to establish and maintain social hierarchy. In non-human primates as well as in humans, staring back at an angry individual is a confrontation for social dominance (Mazur and Booth, 1998). Averting the gaze from threatening eye-contact, on the other hand, is an indicator of subordinate behavior serving to prevent direct or physical confrontation and is linked to high social anxiety traits (Terburg et al., 2016, 2011).

In the current study we use a validated gaze-aversion paradigm to measure the effect of touch on dominant behavior in the context of social confrontation. Using an interactive eye tracking approach, we measure the time it takes participants to actively avert their gaze from eye-contact with angry, happy and neutral faces. Specifically the contrast of eye-contact with angry compared to happy faces has previously been associated with social dominance motives (Enter et al., 2016; Terburg et al., 2016, 2012, 2011). Slower gaze-aversion from angry compared to happy faces thereby reflects social dominance and reduced socially anxious behavior, whereas an increased gaze-aversion speed is related to submissive traits and social anxiety. In addition, socially anxious individuals show a shift from fast to slower gaze-avoidance from angry compared to happy faces after an administration of testosterone. Important in this context, the emotional expressions are presented subliminally which ensures that the gaze-aversion task measures social dominance on an implicit and reactive level (Terburg et al., 2016). With social touch increasing resilience and reducing behavioral tendencies related to social anxiety (Brummelman et al., 2018; Burleson and Davis, 2014; Jakubiak and Feeney, 2016a&b), we expect that social touch increases social dominance as indexed by slower gaze-aversion from unseen angry compared to happy eye-contact.

Methods

Participants

Thirty-two healthy female volunteers participated in the study (age: m = 20.9, SD = 2.3). With the here reported task being part of a larger study, the sample size was determined based on previous studies using a comparable range of tasks and measures (Hofman et al., 2013, 2012; Terburg et al., 2012). Further we conducted a power analysis with medium to large effect size of f=.35 (cf. Hofman et al., 2013, 2012; Terburg, Aarts, & Honk, 2012) for a within-subject repeated measures ANOVA, carried out with G*Power 3 (Erdfelder, 2007; Erdfelder & Buchner, 1996). We chose to include female participants only to avoid sex differences as a confound regarding the touch manipulation, which was done by a female experimenter. All participants included in the study used oral contraceptives, which ensures that hormonal fluctuations do not influence the study results. In total 8 participants were excluded from analysis, resulting in N=24 for the analysis. One participant was excluded due to technical difficulties, one did not attend the second testing session, five participants scored 15 or higher on the emotion awareness check concerning the task stimuli that was conducted after the experiment (details under the paragraph 'Emotion Awareness Check'), and one participant for whom the experiment had to be recalibrated more than 3SD from the mean repositioning rate (m = 4.3, SD = 13.8; defined as amount of times the eye-tracker checks the position of the participant in relation to stimulus presentation). Participants received either monetary rewards or course credits. The study was approved by the ethical committee of the faculty of social sciences of Utrecht University.

Gaze-aversion task

The study was set up as a within-subject cross-over design, each participant attended in total three sessions as part of a larger study. The first session was aimed to be informative on the procedural aspects of the study, it further included several questionnaires, and a measurement of pain threshold/ tolerance which was separated from the experimental sessions to avoid interference with the different tasks. The gaze-aversion task was performed in session two and three, once with prior touch manipulation and once without. Whilst electroencephalography (EEG) and electromyography (EMG) electrodes were placed at the start of session two and three, the here reported task was designed for eye-tracking specifically and does not allow to report EMG or EEG data due to the fast timing of events. The starting order of sessions (touch vs. no-touch) was counterbalanced in random fashion over participants.

The gaze-aversion task started immediately after the touch manipulation, once the experimenter left the room. In the gaze-aversion task three types of emotional stimuli were presented subliminally, displaying happy, angry and neutral facial expressions by 5 male and 5 female actors. A trial developed, starting with a gray pre-mask stimulus with a fixation point at center, followed by a face stimulus displayed in blue, green or red for 27ms and then immediately replaced by a post-mask stimulus presented in the same color as the face stimulus (see Fig. 1). To assure

that masks and stimuli had similar luminance properties, masks were created by cutting-up and randomly reassembling the facial stimuli. During pre-mask display, participants were asked to fixate on the fixation cross, which marked the location of the screen where the eyes of the facial stimulus would appear. The participants gaze was monitored by an eye-tracker to ascertain consistent fixation in the randomly pre-determined time interval (1000, 1500ms) before stimulus presentation. Below the stimulus area three gray same size circles were displayed at equal distance from the fixation point, each of them changing color (blue, green and red at random location) together with post-mask presentation. The participants task was, as soon as the stimulus turned from gray to color, to identify and look as fast as possible from the fixation point to the circle with the corresponding color. The post-mask disappears once the gaze is shifted to the correct corresponding color and therewith ends the trial.

Trials were presented in a fixed sequence (NxxyNyyxNNyyxNxxyN; N = neutral; x and y = angry and happy, counterbalanced across the two sessions) repeated 5 times, which allowed to present all possible combinations of successive facial expressions equal amount of times and therefore preventing trial-by-trail emotion carry-over effects. A total of 90 stimuli (10 actors,

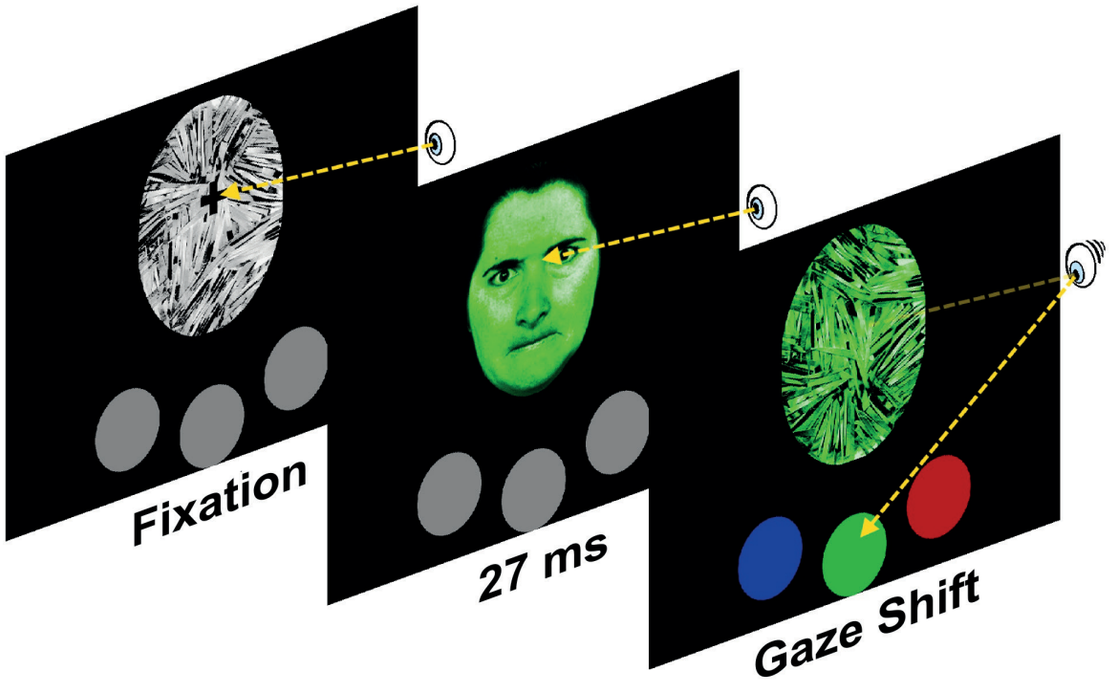

Fig. 1. Example of a trial-based stimulus sequence in the gaze-aversion task. The fixation cross was presented for 1000-1500ms together with the pre-mask. Stimulus presentation is only initiated if the eye-tracker detects continuous gaze on the fixation cross. The face stimulus in one of three colors (blue, green or red) is presented for 27ms, followed by the post-mask in the same color. The grey dots presented under the stimulus area change to color (blue, green and red) in randomized order together with appearance of the post-mask. The mask stimulus disappears once the gaze shifts to the color corresponding dot and therewith ends the trial.

3 expressions, 3 colors) were presented during the task, with 10 additional practice trials with neutral facial expressions at the start of the task. Previous research has shown that the difference in gaze-aversion latency for angry and happy faces is a marker for dominance motives (Enter et al., 2016; Terburg et al., 2016, 2012, 2011).

Emotion awareness check

At the end of the final session, participants were asked to complete a second task in which all 30 faces (10 faces x 3 emotions) were presented again, with backward and forward masking, however this time participants were instructed to identify the emotional valence of the stimulus in a three way forced-choice design. Colors were randomly assigned, however each color was presented 10 times. Emotion awareness was defined as recognition of emotional expressions above chance (>14 correct identification; chance level = 10 correct out of 30; binomial test with one-tailed α=0.05). Important to note is that the awareness check did not screen for awareness of faces, but awareness of emotional expression specifically.

Touch manipulation

The touch manipulation was based on a manipulation used in a recently published study by Brummelman, Terburg, Smit, Bögels, & Bos (2018) investigating the effect of parental touch on social vigilance in children. The standardized procedure looked as follows: Session 2 and 3 both started with preparation of the participant for the different experimental tasks of the study, including placement of electroencephalography (EEG) and electromyography (EMG) electrodes. Next, after starting up the gaze-aversion task, the female experimenter, standing slightly behind the participant on her right, either briefly touched or did not touch the participants shoulder whilst encouraging the participant to start with the experiment. The experimenter subsequently walked out of the room without further interaction. In the touch condition the experimenter placed her left hand on the participant's right shoulder, below the deltoid, for approximately one second (cf. Brummelman et al., 2018). We decided to use a manipulation designed to be short and precise, as well as subtle. Firstly, we were interested in creating a touch scenario that could naturally happen in the laboratory setting, without making the participant uncomfortable. Furthermore, again with the intent of keeping the set up as natural as possible, we aimed for a manipulation that is not consciously perceived by the test subject (cf. Brummelman et al., 2018).

During debrief and manipulation check a total of 11 out of 24 subjects reported that they noticed being touched on the shoulder in the course of the study. 8 of those 11 could report the moment correctly, none of the participants reported the touch as uncomfortable and only 1 person suspected it might be part of the experiment at the end of the last session. Awareness about the touch manipulation included as a between subject factor in a separate 2x3 ANOVA and showed to have no influence on the reported results (all interaction p-values including between subject factor $p > .43$). We therefore did not exclude any of the here mentioned participants from analysis.

Questionnaires

To account for individual differences, we asked participants to fill in the Social Touch Questionnaire (STQ) at the end of the final session, a 20 item scale which measures a broad range of attitudes towards social touch (Wilhelm et al., 2001).

Furthermore, participants were asked to complete the Liebowitz social anxiety scale (LSAS; Safren et al., 1999) questionnaire, which has previously been shown to be predictive for faster gaze-aversion from angry faces in individuals scoring high on the LSAS (Terburg et al., 2016).

Data acquisition and analysis

Eye movements were recorded with a Tobii Pro TX300 infrared eye tracker (Tobii Technology, Danderyd, Sweden) sampling at 300Hz, with 0.4° accuracy. Gaze-aversion latency was defined as the time between the face stimulus onset and the moment the gaze reached the target circle. All latencies that exceeded more than 3 standard deviations of an individual's mean were excluded from the analysis (2.09% of all trials).

The effect of social touch on gaze-aversion latencies is tested in two steps. We first evaluate the touch by emotion interaction using a 2 (touch, no-touch) x 3 (angry, happy, neutral) repeated measures ANOVA, with touch and emotion as within subject factors. If successful, we follow-up by testing the main hypothesis that touch will slow-down gaze-aversion from angry, compared to happy, eye-contact using a 2 (touch, no-touch) x 2 (angry, happy) repeated measures ANOVA, and also test for general touch effects on gaze-aversion from neutral eye-contact using a paired-samples t-test.

To evaluate the influence of STQ and LSAS these analyses are repeated twice, with these questionnaires as respective covariates.

Results

Main analysis

As expected social touch affected gaze-aversion from eye-contact in an emotion specific manner (significant touch x emotion interaction $F(2,46) = 3.99$, $p = .025$, $\eta p2 = .15$, neither a main effect of emotion $F(2,46) = .11$, $p = .895$, $\eta p2 = .01$, nor a main effect of touch $F(1,23) = .31$, $p = .583$, $\eta p2 = .01$). The averages per condition are presented in Table 1. In line with our hypothesis social touch induced slower gaze-aversion from angry compared to happy eye-contact ($F(1,23) = 5.83$, $p = .024$, $\eta p2 = .2$; Fig. 2), and also induced marginally slower gaze-aversion from neutral eye-contact ($t(23) = 2.01$, $p = .056$).

Post-hoc we checked whether the touch-effect on angry and happy gaze-aversion was independent of the touch-effect on neutral gaze-aversion. For this we first computed for each participant the touch-effect on neutral gaze-aversion (touch minus no-touch) and added these values as covariate to the 2 x 2 (touch/no-touch x angry/happy) repeated measures ANOVA.

Results showed that the significant interaction of touch and emotion persisted ($F(1,22) = 7.22$, $p = .013$, $\eta p2 = .25$), confirming that the hypothesized touch-effect on gaze-aversion from angry compared to happy eye-contact is independent from the marginal touch-effect on gaze-aversion from neutral eye-contact.

STQ analysis

To assess whether individual attitudes toward touch predict the effect of touch on gaze-aversion in angry compared to happy faces, we added STQ as a covariate to the 2 x 2 (touch/no-touch x angry/happy) repeated measures ANOVA. The original effect of touch, slowing gaze-aversion from angry compared to happy faces, persisted ($F(1,22) = 5.79$, $p = .025$, $\eta p2 = .21$), and the effect seemed to be independent from attitudes around touch (no significant Touch x Emotion x STQ interaction $F(1,22) = .84$, $p = .370$, $\eta p2 = .04$). At the same time, we found a significant interaction of Emotion x STQ ($F(1,22) = 9.39$, $p = .006$, $\eta p2 = .3$), suggesting an effect of attitudes around touch on gaze-aversion, independent of the touch manipulation itself. Testing the effect of STQ scores separately on each emotion (touch/no-touch x angry, touch/no-touch x happy) confirmed the independence of STQ attitudes from the touch manipulation in both emotions, suggesting rather an effect of attitude towards touch specifically on gaze-aversion from angry compared to happy eye contact. Individuals who are more comfortable with touch (low STQ score) show slower gaze-aversion from angry compared to happy faces compared to individuals who are less comfortable with touch (high STQ score; correlation of angry compared to happy eye contact, touch and no-touch pooled together, correlated with STQ: $r(22) = -.55$, $p = .006$).

LSAS analysis

In a third step we included the Liebowitz Social Anxiety Scale (LSAS) as a covariate in the analysis. Social anxiety had no influence on gaze-aversion behavior with or without touch, no near to significant interaction effects with LSAS were found in the 2 x 2 (touch/no-touch x angry/happy) ANOVA (all $p > .05$).

Discussion

In line with our expectations we show that brief social touch results in slower gaze-aversion from subliminally presented angry compared to happy eye-contact, an index of increased dominant behavior in social situations. Previous literature has shown that social touch reduces both psychological and physiological markers of stress and anxiety (Brummelman et al., 2018; Ditzen et al., 2007; Dunbar, 2010) and promotes confident behavior including exploration, readiness to engage in difficult challenges and risk taking behavior (Jakubiak and Feeney, 2016a; Levav and Argo, 2010). Our study extends those effects found on a psychological and physiological level to implicit and reactive levels of behavior.

Table 1.
Overview of Average Gaze-Aversion Latencies

Condition	Angry	Happy	Neutral
Touch	412.94	402.05	417.3
	95% CI [388.06, 437.84]	95% CI [382.58, 421.51]	95% CI [395.46, 439.15]
No-touch	404.25	412.29	400.8
	95% CI [381.6, 426.9]	95% CI [387.10, 437.47]	95% CI [381.12, 420.5]

Means of gaze-aversion latencies in milliseconds for angry, happy and neutral faces in both, ouch and no-touch condition. 95% Confidence Intervals (CI) are indicated.

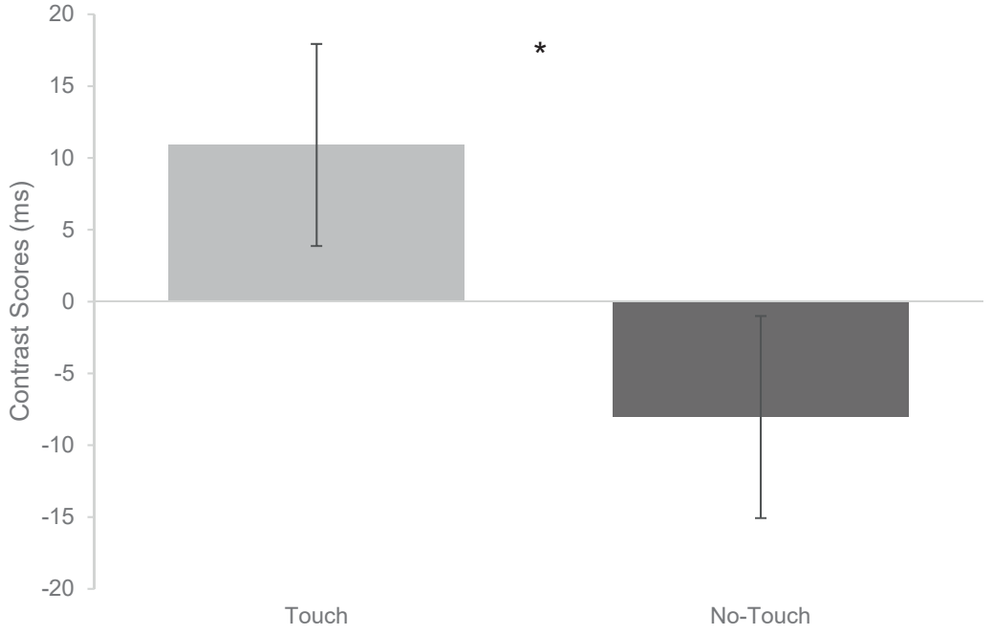

Fig. 2. Contrast scores in milliseconds (ms) of angry compared to happy eye-contact, calculated by subtracting mean happy gaze-aversion latencies from mean angry gaze-aversion latencies separately for the touch and no-touch condition. Social touch resulted in significantly slower gaze aversion from angry compared to happy eye-contact, with * $p < .05$. The error bars represent the standard error of the mean.

In addition to the effect of interest, we found a marginal effect of touch on gaze-aversion from neutral faces, with slower gaze aversion from neutral stimuli after touch. Importantly, the effect was independent from the touch-effect on angry compared to happy faces. A possible interpretation of why touch affects gaze to neutral faces in the same direction as angry faces (cf. Table 1) is that neutral facial stimuli are ambiguous social stimuli and therefore categorized as potentially threatening rather than safe (Lee et al., 2008).

Analyses of covariance showed that the found main effect is independent from attitudes around touch (STQ) and markers of social anxiety (LSAS). To start with the latter, our results support Brummelman et al. (2018) who showed that LSAS moderates the effect of touch on trustworthiness decisions, but not on implicit reactions to threat as also measured here. Further, interesting for future research is that we found that participants who report to be relatively uncomfortable with social touch are more avoidant in their gaze-aversion behavior in angry compared to happy eye contact. The main finding of interest, the influence of touch on gaze-aversion in angry compared to happy faces, was however not affected by this interaction of STQ with gaze-aversion behavior.

Looking at the possible underpinnings of gaze behavior when conscious processing of the stimuli is prevented, a structure suggested to mediate gaze-aversion is the amygdala. It has been shown to mediate fear and aggression related reflexes in human and non-human primates through its output connections to other subcortical structures, specifically the hypothalamus and brainstem (Davis and Whalen, 2001; Terburg et al., 2016). Considering the neural underpinnings of social touch in general, the amygdala, amongst other regions, is important to process and code the emotional value of touch and to facilitate the further integration of touch through cortical areas (Boehme et al., 2018). Furthermore, touch has been associated to the release of endogenous opioids (Coan et al., 2006; Ellingsen et al., 2016; Morrison, 2016). Opioids have been shown to be involved in the regulation and deactivation of areas responsible for threat and fear processing such as the amygdala (Eippert et al., 2008; Haaker et al., 2017) and therefore are an interesting candidate to consider when looking at the underpinnings of the psychological and behavioral effects of touch.

Last, a clear strength of our study is the touch manipulation. The manipulation is a form of social touch to be found in day to day life and still, partly due to its implicitness, was easy to implement in the experimental context. The manipulation has previously shown to be effective in parent-child context (Brummelman et al., 2018) and now in the context of an unfamiliar other situation. Taken together, the social and implicit aspect of the touch manipulation increase the external validity of the study compared to other approaches, such as using a brush to induce optimal C-tactile afferent stimulating touch. Limitations of the current study are that whilst the

findings give us an indication about the momentary effects of touch, it does not take long-term effects into account. Another limitation is that this study included female subjects only. Whilst the task has previously been applied in mixed (Hortensius et al., 2014; Terburg et al., 2011) as well as female only samples (Terburg et al., 2012, 2016) without showing sex specific differences in task performance, a sex specific effect of touch might exist. Further, we decided for a same-sex experimental set up with a female experimenter implementing the manipulation. It would therefore be important to test for the generalizability of the results in the male population as well as for potential differences in a set up with a same-sex compared to other-sex experimenter in future studies.

Conclusion

Using an interactive eye-tracking approach, we show that brief social touch by a stranger increases social dominance behavior in female participants, characterized by slower gaze-aversion from subliminally presented angry compared to happy eye-contact (Brummelman et al., 2018; Terburg et al., 2016, 2012, 2011). These results provide evidence that touch adds to psychological resources useful in challenging situations through increased implicit tendencies to engage in social confrontations.

Chapter 6

General Discussion

Summary and discussion

The aim of this thesis was to investigate aspects of social-emotional behavior that contribute to social affiliation and protect from the aversiveness of negative social experiences, while focusing on opioid and oxytocin systems. One main premise of the thesis is that social behaviors which support bonding and affiliation are based on fundamental mechanisms of pain and reward processing and regulated by opioid and oxytocin systems.

Chapter 2 starts with a framework on the role of the mu-opioid receptor (MOR) system in social-emotional behavior, which suggests that the MOR system influences social processing through its key function of attributing hedonic value to social cues of pain and reward, and therewith impacts more complex social behaviors and abilities. It has been suggested that pain and pleasure act mutually inhibitory on each other through opioid modulation which allows prioritization of behaviors most relevant for survival (Fields, 2006; Leknes and Tracey, 2008). Based on this idea we developed the 'Mu-opioid feedback model of social behavior', a heuristic model which suggests that the MOR system attributes the hedonic value to social cues by acting on reward and threat related neural networks in the brain. Depending on the hedonic interpretation of the social cue, the individual experiences a sense of pleasure or pain. Pleasure promotes social exploration and affiliation, whereas pain is followed by a reduction in reward sensitivity and social exploration, and therefore promotes behavioral (comfort seeking) and neural mechanisms of pain relief. The model further discusses the consequences of an imbalance in MOR modulation caused by (early life) traumatic experiences or chronic stress. Based on animal research and human research on substance abuse (Garland et al., 2019, 2017; Savulich et al., 2017; Valentino and Van Bockstaele, 2015) we suggest that a dysregulation of the MOR system through chronic stress results in a shift toward protective mechanisms and behaviors. These protective mechanisms are adaptive in the acute situation (reduced reward sensitivity, reduced exploration, pain relief), but in the long-term they negatively affect the formation and maintenance of social bonds and therefore leave the individual at increased risk for prospective stress, for substance abuse- and mood disorders.

The literature reviewed in chapter 2 lays the foundation for the 'Mu-opioid feedback model of social behavior'. Starting from the point of MOR modulation of pain, research provides evidence that the MOR system's inhibitory role in pain extends to the social domain, serving a protective function in the face of distress. In the context of social rejection opioids are released in areas associated with pain processing, resulting in reduced negative affect (Hsu et al., 2013). Further, the MOR system seems to inhibit neural markers of pain processing when seeing other's in pain (Rutgen et al., 2015), potentially reducing personal distress similar to oxytocin (as discussed in chapter 4). Closely related to its effects on (social) pain, the MOR system inhibits processing of threat cues and threat related learning (Eippert et al., 2008; Haaker et al., 2017; McNally, 2009) (see Fig. 1). It further has been shown to reduce the subjective and physiological stress response in humans and rodents (Bershad et al., 2015; Drolet et al., 2001; Ribeiro et al., 2005).

On the other hand, several studies in humans and non-human animals support the idea that the MOR system modulates the hedonic component of pleasure and reward (Buchel et al., 2018; Chelnokova et al., 2014; Trezza et al., 2010; Vanderschuren et al., 1995). Opioids have been shown to regulate the subjective liking of, and the neural response to, high-reward value images in humans (Buchel et al., 2018; Chelnokova et al., 2014) and additionally seem to modulate the behavioral motivational component toward these stimuli (Chelnokova et al., 2014). Based on the idea that affiliation is in part driven by basic reward mechanisms that facilitate approach (Herman and Panksepp, 1978; Panksepp et al., 1980), as discussed in our model in chapter 2, in chapter 3 we investigated whether the MOR system regulates an underlying, automatic behavior of social affiliation: the congruent emotional mimicry of facial expressions. Indeed, we found MOR regulation of facial responses to happy faces, social reward cues that communicate social acceptance and invite for approach (see Fig. 1). More specifically, blocking the MOR system with naltrexone disrupted the congruent imitation of happy facial expressions by activating facial muscles associated with negatively-valenced emotions such as sadness and anger. Since congruent mimicry of social reward signals has been shown to promote affiliation (Lakin and Chartrand, 2003) we suggest that the MOR system has a central role in regulating the underlying mechanisms of appetitive responses to social reward cues, and hereby affects social affiliation and attachment. Indeed, other studies support this idea. MOR activation in the ventral striatum, a main hub for reward processing (Berridge and Kringelbach, 2013; Peciña et al., 2006), is predictive for the desire of social interaction (Hsu et al., 2013). Further, administration of naltrexone consecutively over several days was shown to decrease the feeling of social connection (Inagaki et al., 2016).

As suggested in the 'Mu-opioid feedback model of social interaction' in chapter 2, opioid regulation at the level of social cue processing in reward and threat related neural networks influences social learning, motivation and memory formation which in turn affects affiliative motivation. Whereas the MOR system seems to regulate social behavior through modulation of the hedonic quality of social cues and interactions, another well-known modulator of social behavior, oxytocin, has been suggested to do so by regulating salience perception (Olff et al., 2013; Shamay-Tsoory and Abu-Akel, 2016). Chapter 4 investigates the role of the oxytocin system in neural sensitivity to social reward and affective empathy towards children. Both empathy and reward sensitivity are fundamental components of caregiving behavior, promoting parent-infant communication and interaction, as well as recognition of the child's needs (Bos, 2017). We found that reported history of childhood emotional neglect (EN) was predictive for the effects of oxytocin on neural reactivity in the amygdala and hippocampus, and in prefrontal regions (see Fig. 1). Low reactivity to positive and neutral images in the amygdala and hippocampus of high EN subjects after placebo, was increased by oxytocin to the level of low EN subject. In prefrontal regions oxytocin reduced activation to neutral stimuli in high EN subjects, suggesting a decrease in regulatory prefrontal control. These results imply that early life stress

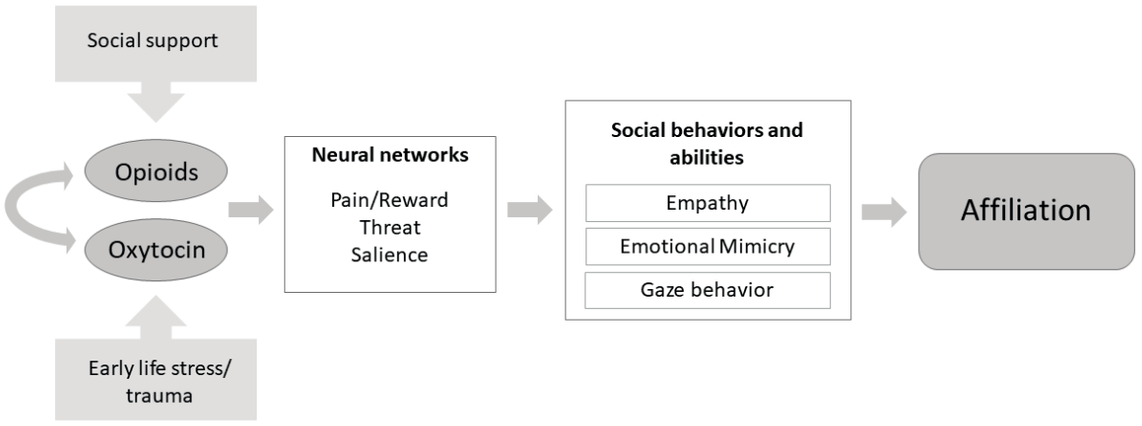

Fig 1. The framework of the thesis can be seen in Figure 1. Opioids and oxytocin (inter)act on neural networks involved in fundamental pain- and reward-, threat- and salience processing. By regulating basic emotional processes, opioids and oxytocin act on social behaviors and abilities that are central in social affiliation. Early life stress or the experience of trauma change the sensitivity of the opioid and oxytocin system in distinct ways, leading to consequences for neural reactivity and behavior later in life. Social support mechanisms such as touch trigger opioid and oxytocin release and therewith affect neural responses and behaviors that contribute to affiliation.

changes the sensitivity to oxytocin with consequences for social behavior later in life (Kraaijenvanger et al., 2019; Nawijn et al., 2019). Indeed, previous studies have shown that early-life adversities (ELA) as well as other stressful events in adulthood can reduce the positive effects of oxytocin on physiological stress reactivity (Meinlschmidt and Heim, 2007). Further, ELA were related to changes in neural responses during resting state (Fan et al., 2014; Frijling et al., 2016), under stress (Fan et al., 2015; Grimm et al., 2014), and to changes in neural reactivity to different emotional cues (Frijling et al., 2015; Koch et al., 2016).

The sensitivity of oxytocin to stressful events throughout life is an interesting aspect to consider regarding the interactive role of oxytocin and opioids in social behavior. With animal research indicating that chronic stress creates a shift toward MOR inhibitory mechanisms leading to tolerance and dependence (Valentino and Van Bockstaele, 2015), and oxytocin inhibiting opioid tolerance (Kovacs et al., 1987), changes in sensitivity to oxytocin due to early life stress or traumatic events later in life (chapter 4) could facilitate a shift toward dysregulated opioid mechanisms with consequences for social behavior and affiliation (as discussed in our model in chapter 1). In support of this line of thought, early-life stress seems to increase vulnerability for substance abuse later in life. However, strong social bonds within a social support network have been shown to protect from addiction suggesting that recurrent release of oxytocin might maintain the sensitivity to opioid mediated social reward mechanisms (Panksepp et al., 1994).

This leads the discussion to social touch, which is considered a social support mechanism and

a booster of social affiliation through its pleasurable quality (see Fig. 1). Indeed, touch is argued to reduce physiological markers and subjective perception of stress (Ditzen et al., 2007; Jakubiak and Feeney, 2016a; Morrison, 2016), attenuate the attentional bias to threat in children (Brummelman et al., 2018), and to increase feelings of security and social exploration (Jakubiak and Feeney, 2016a&b). In chapter 5 we investigated the effects of social touch on gaze behavior as a marker of social motivation. The speed of gaze-aversion from subliminally presented affective stimuli has previously been associated with social dominance/submissive motives (Terburg et al., 2012, 2016). In chapter 5 we show that touch indeed functions as a social buffer, increasing gaze behavior associated with dominance motives and reduced socially anxious behavior. The opioid and oxytocin system are interesting candidates when it comes to the possible underpinnings of the beneficial effects of touch. Touch has been associated with endorphin and oxytocin release in humans and non-human primates (Dunbar, 2010; Ellingsen et al., 2016; Morrison, 2016). Both neuropeptides act on the hypothalamic-pituitary-adrenal (HPA) axis and have been associated with stress reducing effects (Bershad et al., 2015; Olff et al., 2013). Further, pleasant touch reduced reactivity of facial muscles related to negative facial expression (Mayo et al., 2018). This effect could be opioid mediated based on our findings in chapter 2 which showed that MOR blockade results in increased activity in this muscle. However, as discussed in chapter 1 & 2, effects of administration studies on touch involving either system are less conclusive, warranting further research.

Closing thoughts and future directions

A variety of complex factors are involved in social affiliation, the intertwined relationship between an individual's neurobiological setup and its life experiences shape the neural sensitivity to social cues in the environment which in turn influences social behavioral responses that contribute to social affiliation. This thesis makes a contribution to the body of literature that outlines the importance of investigating the underlying neurobiological mechanisms of social behavior.

In two studies directly manipulating the opioid and oxytocin systems, we observed opioid modulation of emotional mimicry, an underlying automatic behavior contributing to affiliation (chapter 3), and for the first time in women, oxytocin modulation of neural reactivity toward emotional cues from children on the level of amygdala, hippocampus and prefrontal regions, depending on childhood EN (chapter 4). Furthermore, we found that social touch increases gaze behavior associated with social dominance and low anxiety, supporting evidence showing that touch acts as a social buffer (chapter 5). As such the thesis contributes to the field of social neuroscience with evidence on the underlying neurobiological and behavioral mechanisms of social affiliation. At the same time, the work described here also creates inspiration for future research. Starting with the research discussed in the theoretical framework of the 'Mu-opioid feedback model of social behavior' in chapter 2, an obvious question with respect to opioid

modulation of social behavior would be, whether MOR effects in humans depend on early-life adversities. Animal research supports the idea that chronic stress alters acute stress response mechanisms toward chronic opioid inhibition (Valentino and Van Bockstaele, 2015), however human data is lacking. At the same time, considering the reviewed literature in chapter 2, there are a considerable number of fundamental research questions on the effects of the MOR system that need answering. For example, it is still unclear to what extent MOR effects on motivational aspects of reward rely on dopaminergic input. Further, rodent and human literature suggest an inhibitory role for the MOR system in threat related association learning, but animal research demonstrating a facilitatory role of the MOR system in extinction learning of threat (McNally and Westbrook, 2003) is still to be replicated in humans. Extinction learning is a crucial emotion regulation strategy often found to be impaired in mood or stress related disorders such as anxiety and PTSD. Investigating the role of the MOR system in this context could therefore contribute to the understanding of these disorders and the fundamental mechanisms of threat extinction itself. The discussed research in this thesis and the emerging questions outline the value of translational research especially in the field of psychopharmacology, and further of paradigms that integrate behavioral as well as physiological approaches.

In chapter 4 we show for the first time in women that oxytocin effects on neural reactivity toward emotional signals from children are dependent on early life experiences. The results suggest that in a sub-clinical sample, oxytocin administration could have beneficial effects by increasing the salience of social reward signals from children. At the same time, it leads toward the question whether oxytocin effects differ from the current results in individuals who experienced severe emotional neglect during childhood. Previous research in PTSD patients and healthy trauma exposed controls showed increased neural reactivity in the amygdala with oxytocin in the control group, in line with our own results, but decreased reactivity in the PTSD group (Koch et al., 2016). This points toward differences in changes of oxytocin sensitivity, possibly depending on trauma severity, resilience or social support mechanisms.

With regard to the findings in chapter 5, future research should further investigate the underlying neurobiology of touch, using a touch manipulation that conveys social meaning and paradigms that asses the subjective experience of touch (pleasantness/intensity), as well as a combination of behavioral and physiological responses to touch. For a start, it would be interesting to investigate whether the social buffering effects of touch on gaze behavior are opioid mediated and could therefore be blocked by administration of naltrexone. Furthermore, one might consider studying whether naltrexone could block the physiological stress buffering effects of touch found on cortisol response, heat-rate variability (Ditzen et al., 2007) and neural reactivity to threat (Coan et al., 2006).

Finally, examples like the ongoing opioid-crisis in North America outline the importance of investigating the role of the endogenous neurobiological systems in social behavior. In depth knowledge of neurobiological systems that drive perception, motivation and behavior will help

in understanding disorders like addiction, and therewith contribute to identification of risk factors, protective mechanisms and better treatment. The title of this thesis 'Touching upon affiliation' hints toward the fact that even though research has contributed a considerable amount of knowledge on the underlying mechanisms of social behaviors, including affiliation, we are only just touching the surface of what is to be explored.

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Author Contributions

Chapter 2: A mu-Opioid Feedback Model of Human Social Behavior

Author IMM drafted the manuscript and DT, JvH and PAB provided critical revisions. All authors have approved the final manuscript.

Chapter 3: Naltrexone increases negatively-valenced facial responses to happy faces in female participants

Author PAB, JvH & SMS designed the study and wrote the protocol. Author KH conducted the experiment. Author IMM and PAB managed the literature searches and facilitated data analyses. Authors IMM and PAB undertook the statistical analysis, and authors IMM, PAB, DJS, JvH & SMS contributed to the writing of the manuscript. All authors contributed to and have approved the final manuscript.

Chapter 4: Oxytocin increases reactivity in the amygdala and hippocampus to emotional stimuli of children in women depending on childhood emotional neglect

PAB and ERM developed the study concept and design. HS collected the data which then was checked by HS and SO. IMM, SO and PAB performed the data analysis. IMM drafted the manuscript, PAB, ERM and JvH provided critical revisions. All authors approved the final version of the manuscript.

Chapter 5: Social touch increases dominant gaze in social confrontations

IMM, PAB and JvH developed the study concept. All authors contributed to the study design. IMM led and supervised data collection. IMM and DT performed the data analysis. IMM drafted the manuscript, DT, PAB and JvH provided critical revisions. All authors approved the final version of the manuscript for submission.

Nederlandse Samenvatting/
Summary in Dutch

Mensen zijn sociale dieren. Andere dieren zijn sneller, sterker, hebben het voordeel van een beter ruikvermogen of zicht dan mensen. Omdat we om te overleven afhankelijk van elkaar zijn, zijn complexe sociale vaardigheden belangrijk en noodzakelijk voor communicatie, het vormen en onderhouden van sociale relaties, oplossen van conflicten en samenwerking. Deze verfijnde vaardigheden komen met een bepaalde kwetsbaarheid: de ervaring uitgesloten te worden door een vriendengroep of partner is bijzonder pijnlijk, zelfs lichamelijk waarneembaar als een pijn of druk in de borst. Sociale isolatie en eenzaamheid activeren stress en gerelateerde psychologische en neurobiologische mechanismen, en wanneer ze voor een langere periode ervaren worden zijn ze risicofactoren voor fysieke en mentale gezondheidsproblemen. De aversie voor de ervaring van sociale afwijzing, waarvan bekend is dat het neurale netwerken activeert die gerelateerd zijn aan de verwerking van pijn, wordt gezien als motiverende factor voor het individu om troost te zoeken en het aanpassen van gedrag voor een succesvollere strategie voor sociale binding. Aan de andere kant, het gevoel dat uitgelokt wordt door het samenzijn met dierbaren, een knuffel van een vriend, of het zien van een glimlach op het gezicht van een kind, is belonend en wordt omschreven als een warm, comfortabel en plezierig gevoel. Het belonende gevoel van sociale interacties zorgt voor het vormen van sterke sociale relaties die op de lange termijn als een beschermende buffer tegen stress kunnen optreden. Het is daarom niet verassend dat de complexe gedragingen en vaardigheden die nodig zijn voor het ondersteunen van verbondenheid, en ons en anderen beschermen in onze sociale omgeving, zoals het vermogen om de intenties en gevoelens van anderen te begrijpen, gebaseerd lijken te zijn op dezelfde mechanismen die betrokken zijn bij pijn en genot. Twee neurobiologische systemen die betrokken zijn bij zowel pijn als genot, en cruciaal zijn voor het vormen en onderhouden van relaties met anderen, zijn de oxytocine en opioïde systemen.

Het veld van de sociale neurowetenschappen richt zich op de neurale en neurobiologische factoren die sociaal-emotioneel gedrag mogelijk maken, en combineert vragen en experimentele methoden van het veld van de sociale psychologie met de verschillende aanpakken uit de velden neuroendocrinologie, affectieve neurowetenschap, psychofarmacologie en gedragsgenetica.

Deze thesis tracht de aspecten van sociaal-emotioneel gedrag te onderzoeken die bijdragen aan sociale verbondenheid en bescherming van het individu tegen aversieve reacties als gevolg van sociale afwijzing en isolatie, met een focus op de rol van de oxytocine en opioïde systemen. Er zijn basale, automatische en complexere, hogere-orde processen die motivatie voor sociale verbondenheid moduleren. In deze thesis zal ik me richten op twee processen die bijdragen aan verbindend gedrag; emotioneel spiegelen, de automatische faciale reactie op het zien van de emotionele expressies van iemand anders (Hoofdstuk 3), en kijkgedrag als marker voor sociale motivatie (Hoofdstuk 5). Ook zal ik twee componenten van sociaal-emotionele communicatie onderzoeken die essentieel zijn voor verbondenheid en sociale buffering: empathie, het vermogen om de emoties van anderen te lezen, begrijpen en delen (Hoofdstuk 4) en aanraking, dat via plezierige en belonende kwaliteiten als een buffer tegen sociale pijn functioneert (Hoofdstuk 5).

Opioïde en oxytocinerge modulatie van sociaal-emotioneel gedrag

Morfine, het actieve ingrediënt van opium, dat weer een extract is van de opium papaver Papaver somniferum, werd voor het eerst geïsoleerd door Sertürner in 1804. Echter, de eerste aanwijzingen voor het gebruik van opium gaan terug naar de Sumeriërs in 3000 v.Chr., wat impliceert dat het werd gebruikt voor zowel rituele en recreatieve, als medicinale doeleinden. De pijnstillende effecten van het mu-opioïde systeem (MOR), waarmee de effectieve pijnstiller morfine zijn effecten bewerkstelligd, maakten het MOR-systeem een interessant doelwit voor onderzoek binnen de medische, en hierop volgend, sociale wetenschappen. Mu-opioïde receptoren kennen een wijdverspreide distributie door het gehele brein, met hoge concentraties in gebieden die betrokken zijn bij beloning en verwerking van pijn, zoals het ventrale striatum, periaqueductal grijs, substantia nigra, thalamus, amygdala, hippocampus, en corticale gebieden zoals de cingulate- en prefrontale cortex. De euforische eigenschappen van opioïden en hun rol in verslaving kregen veel aandacht, maar bemoeilijkten het onderzoek naar de sociale eigenschappen van opioïden vanwege ethische bezwaren. Echter, eerder dieronderzoek suggereert een meer diverse rol voor endogene opioïden, bijvoorbeeld in het mediëren van affect, sociaal gedrag en hechting. Meer recentelijk is de sociale neurowetenschap de potentie van endogene opioïden bij de mens aan het exploreren, door de functie van het MOR-systeem te onderzoeken. Dit onderzoek demonstreert dat opioïden inderdaad de belonende componenten van affect, affectief leren en geheugen beïnvloeden, en daarmee bijdragen aan gedrag en vaardigheden zoals empathie, die sociale verbinding stimuleren.

Een ander systeem dat bekend staat om zijn prominente rol in sociale verbinding en diverse effecten op sociaal gedrag is het oxytocine systeem. Oxytocine is een neuromodulator die wordt gesynthetiseerd in de paraventriculaire en supra optische nuclei van de hypothalamus. Vanuit de hypothalamische nuclei projecteren neuronen direct naar target gebieden in het centrale zenuwstelsel (CZS), zoals de amygdala en de nucleus accumbens (Nacc), waar de centrale effecten van oxytocine plaatsvinden. De neuronen projecteren verder naar de posterieure hypofyse waar oxytocine wordt vrijgelaten in de bloedstroom en perifere effecten kan bewerkstelligen. Oxytocine staat bekend om zijn essentiële rol bij ouder-kind hechting, zo wordt het bijvoorbeeld vrijgelaten tijdens de bevalling en borstvoeding, en bij partner -voorkeur en - binding. Daarnaast heeft oxytocine pijnstillende en anxiolytische eigenschappen, en reguleert het een breed scala aan sociaal gedrag zoals sociale perceptie en leren, samenwerken en vertrouwen, verschillende componenten van empathie, en emotieregulatie. Een belangrijk aspect om hierbij in beschouwing te nemen, is dat de effecten van oxytocine sterk afhankelijk zijn van de context en van individuele factoren. Olff et al. (2013) stelden dat de waargenomen ‘veiligheid’ van een omgeving de functie van oxytocine en het daarbij behorende gedrag moduleert, en zowel defensief (waargenomen negatieve/onveilige omgeving) en prosociaal gedrag kan faciliteren die sociale verbinding kunnen bevorderen (waargenomen positieve/veilige omgeving). Op het niveau van individuele factoren zou oxytocine selectief sociale vaardigheden kunnen verbeter-

en in individuen met sociale deficiënties, mogelijk door aandacht te verhogen voor relevante sociale cues.

Overzicht van deze thesis

Deze thesis is samengesteld uit een theoretisch overzicht (review) en drie experimentele studies. Beginnend met het review en theoretische perspectief op de rol van het endogene MOR-systeem bij sociaal-emotioneel gedrag, presenteert hoofdstuk 2 een 'Mu-opioïde feedback model van sociaal gedrag'. Het model suggereert dat het MOR-systeem, via zijn sleutelrol in het toewijzen van belonende waarde aan positieve en negatieve sociale stimuli, verbindende en beschermende responsen naar sociale stimuli reguleert, met lange termijn consequenties voor sociaal gedrag en mentale gezondheid.

Hoofdstuk 3 behandelt de vraag of het farmacologisch blokkeren van het MOR systeem met behulp van naltrexone de imitatie van emotionele gezichtsuitdrukkingen, een automatische gedragsmarker van sociale verbinding, verstoort. Via faciale elektromyografie (EMG) werden faciale reacties gemeten in een dubbelblind, placebo-gecontroleerd tussen-proefpersonen design. Omdat opioïden de subjectieve plezierigheid van sociale beloning mediëren, alsmede het gevoel van sociale verbinding, verwachtten we dat het MOR-systeem ook de onderliggende gedragsmatige responsen naar affectieve cues en sociale verbinding reguleert.

Oxytocine is cruciaal voor verzorgen en de perceptie van sociale signalen in kinderen. Onderzoek suggereert echter dat vroege ongunstige ervaringen kunnen resulteren in langdurende veranderingen in neuraal, endocrinologisch en sociaal functioneren, wat de effecten van oxytocine kan moduleren. In hoofdstuk 4 wordt daarom het effect van oxytocine onderzocht op de gevoeligheid voor belonende signalen van kinderen evenals de affectieve empathische reacties naar kinderen in onveilige situaties. Oxytocine toediening werd vergeleken met placebo in een dubbelblind, binnen-proefpersonen design waarin gebruikt werd gemaakt van functionele magnetische resonantie (fMRI). Daarnaast werd gekeken of motivatie voor ouderlijke zorg of vroege negatieve ervaringen de effecten van oxytocine op sociale beloning en empathie moduleerde.

Het laatste experimentele hoofdstuk, hoofdstuk 5, beschrijft een studie waarin we de effecten van aanraking op kijkgedrag naar subliminaal aangeboden emotionele stimuli onderzochten. We gebruikten infrarood eye-tracking om de effecten te onderzoeken van aanraking op snelheid van kijk-aversie van oogcontact, een impliciete marker van dominant-onderdanig gedrag. In voorgaande studies rapporteerden we langzamere kijk-aversie van subliminaal aangeboden angstige gezichtsexpressies in proefpersonen met hoge niveaus van sociale dominantie en lage niveaus van sociale angst. De gunstige effecten van aanraking als sociale buffer, waaronder stress vermindering, reduceerden de bias naar dreiging, verhoogden verkenning en gevoel van veiligheid, en induceren daarom mogelijk een impliciete neiging om sociale uitdagingen aan te gaan, consistent met dominant sociaal gedrag.

Deutsche Zusammenfassung/
Summary in German

Der Mensch ist ein soziales Tier. Und das muss er sein, um in der Evolution mithalten zu können: Andere Tierarten sind schneller, stärker und haben den Vorteil eines besseren Geruchs- oder Sehsinns als der Mensch. Da wir zum Überleben voneinander abhängig sind, sind komplexe soziale Fähigkeiten, die das Zusammenleben ermöglichen essentiell: Kommunikation, Bildung und Aufrechterhaltung sozialer Bindungen, Konfliktlösung und Zusammenarbeit. Diese unglaublich wichtigen und komplexen Fähigkeiten machen uns auf andere Weise jedoch anfällig. Die Erfahrung, von einer Gruppe von Freunden ausgeschlossen oder von einem Partner abgelehnt zu werden, ist bemerkenswert schmerzhaft und kann auf der körperlichen Ebene mit Gefühlen von Atemnot und Schmerzen in der Brust erfahren werden. Langfristig sind soziale Isolation und empfundene Einsamkeit bekannte Risikofaktoren für die körperliche und geistige Gesundheit, und aktivieren stressbedingte psychologische und neurobiologische Mechanismen. Die Aversion gegenüber sozialer Ausgrenzung, motiviert den Einzelnen dazu Sicherheit und Trost im sozialen Umfeld zu finden und möglicherweise auch dazu, sein Verhalten an erfolgreichere Strategien für soziale Bindung anzupassen. Gleichzeitig ist das Gefühl wenn wir Zeit mit Freunden oder Familie zu verbringen, eine Umarmung von einem/r guten Freund/in zu erhalten oder das Lachen des eigenen Kindes zu hören in sich selbst belohnend. Das lässt sich leicht an dem Gefühl von Wärme, Entspannung und einer gewissen Leichtigkeit erkennen. Diese Freude an zwischenmenschlicher Interaktion führt zu stärkerer sozialer Bindungen und schütztlangfristig vor den negativen Effekten von Stress. Es ist daher nicht verwunderlich, dass komplexe sozial-emotionale Verhaltensweisen, die zur Bindung notwendig sind, wie beispielsweise die Fähigkeit die Absichten und Gefühle anderer zu verstehen, von grundlegenden Systemen unterstützt werden die mit der Verarbeitung von Schmerz sowie Belohnung und Genuss verbunden sind. Zwei neurobiologische Systeme von denen gezeigt wurde, dass sie sowohl an der Schmerz- als auch an der Belohnungsverarbeitung beteiligt und für die Herstellung und Aufrechterhaltung von Bindungen mit anderen von entscheidender Bedeutung sind, sind das Oxytocin- und das Opioidsystem.

Das Ziel dieser Doktorarbeit ist es systematisch Aspekte des sozial-emotionalen Verhaltens zu untersuchen die zur sozialen Zusammengehörigkeit beitragen und den Einzelnen vor den aversiven Folgen von Ablehnung und Isolation schützen. Der Schwerpunkt der Doktorarbeit liegt dabei auf der grundlegenden Rolle der Oxytocin- und Opioidsysteme im menschlichen Verhalten, von autmatisch, grundlegendem Verhalten zu komplexeren, kognitiven Prozessen. Diskutiert werden dabei Mimik und Imitation emotionaler Gesichtsausdrücke (Kapitel 3) und Blickverhalten im sozialem Kontext (Kapitel 5), im Hinblick auf soziale Bindung. Darüber hinaus werde ich zwei zentrale Komponenten der sozial-emotionalen Kommunikation untersuchen: Empathie und Berührungen. Empathie, die Fähigkeit die Emotionen anderer zu lesen, zu verstehen und zu teilen (Kapitel 4) ist essentiell bei der Entsehung von sozialen Beziehungen. Genauso wie Berührungen, welche im tagtäglichen Leben eine grundlegende Kommunikationsfunktion haben, und die des weiteren eine wichtige Funktion als Puffer für (sozialen) Schmerz und Stress innehaben (Kapitel 5).

Opioid- und Oxytocin-Modulation des sozial-emotionalen Verhaltens

Morphin, der aktive Wirkstoff in Opium (welches selbst ein Extrakt aus dem Schlafmohn Papaver somniferum ist) wurde erstmals 1804 von Friedrich Sertürner extrahiert. Historisch gesehen, gehen die frühesten Aufzeichnungen über die Verwendung von Opium jedoch auf das Volk der Sumerer im Jahr 3000 v. Chr. zurück. Aufzeichnungen beschreiben die Verwendung von Opium sowohl für rekreativen Gebrauch und Rituale, als auch für medizinische Praktiken. Das hocheffiziente Schmerzmittel Morphin übt seine Wirkung vor allem über das endogene Mu-Opioid-Rezeptor (MOR)-System im menschlichen Körper aus. Es ist diese schmerzlindernde Wirkung die das MOR-System zu einem Ansatzpunkt und interessanten Ziel für die medizinische und anschließend die Sozialforschung gemacht haben. Mu-Opioid-Rezeptoren sind weitreichend im Gehirn verteilt, mit einer hohen Konzentration in Bereichen die an der Belohnung und Schmerzverarbeitung beteiligt sind, einschließlich dem ventralem Striatum, dem periaquäduktalem Grau, der Substantia nigra, dem Thalamus, der Amygdala, dem Hippocampus und kortikalen Bereichen wie dem cingulären und präfrontalen Cortex. Das menschliche endogene Opioid System hat durch die den Opiaten zugschriebenen euphorischen Eigenschaften, aber auch durch deren hohes Suchtpotential viel Aufmerksamkeit in den Medien und der medizinischen Forschung erhalten. Dies hat jedoch auch die Erforschung der Rolle des MOR Systems im sozialen und emotionalen menschlichen Verhalten aus ethischen Gründen erschwert.

Tierversuche deuten daraufhin das endogene Opioide eine vielfältigere Rolle bezüglich Affekt, sozialem Verhalten und Bindung haben. In den letzten Jahren hat das Forschungsfeld der sozialen Neurowissenschaften begonnen das Potenzial menschlicher endogener Opioide, besonders des MOR-Systems, zu untersuchen. Die Forschung hat bisher gezeigt, dass Opioide tatsächlich die hedonische Komponente von Affekt, affektive Lernprozessen und das Gedächtnis beeinflussen, und damit zu Verhaltensweisen und Fähigkeiten beitragen die im sozialen Zusamenleben essentiell sind (z.B. Empathie).

Ein weiteres neurobiologisches System, das für seine Rolle in der Bildung von zwischenmenschlichen Beziehungen und für seine vielfältigen Auswirkungen auf das Sozialverhalten bekannt ist, ist das Oxytocin-System. Oxytocin ist ein neuromodulatorisches Hormon, das in den paraventrikulären und supraoptischen Kernen des Hypothalamus synthetisiert wird. Von den hypothalamischen Kernen projizieren Neuronen direkt zu Zielregionen im Zentralnervensystem (ZNS), einschließlich der Amygdala und des Nucleus accumbens (Nacc), und weiter zur hinteren Hypophyse, von wo aus Oxytocin in den Blutkreislauf freigesetzt wird und anschließend periphere Effekte ausübt. Oxytocin, das während der Geburt und Stillzeit freigesetzt wird, ist bekannt für seine wesentliche Rolle bei der Eltern-Kind-Bindung und bei der Partnerpräferenz und -bindung. Oxytocin hat ferner analgetische und anxiolytische Eigenschaften und reguliert eine ganze Reihe sozialer Verhaltensweisen, einschließlich sozialer Wahrnehmung und Lernen, Kooperation und Vertrauen, verschiedener Komponenten von Empathie und Emo-

tionsregulation. Es ist jedoch wichtig zu berücksichtigen, dass die Wirkungen von Oxytocin stark vom Kontext und individuellen Faktoren abhängen. Olff et al. (2013) schlugen vor, dass die wahrgenommene „Sicherheit" einer Situation die Funktion von Oxytocin und die damit verbundenen, geäußerten Verhaltensweisen moduliert. Beispielsweise, kann Oxytocin entweder defensive (im negativ / unsicher wahrgenommener Kontext) oder pro-soziale Verhaltensweisen (im positiv / sicher wahrgenommener Kontext) fördern.

Tritt man einen Schritt zurück und betrachtet die Grundlagen des sozial-emotionalen Verhaltens des Menschen, dann wird deutlich, dass diese Verhaltensweisen auf Mechanismen der Schmerz- und Belohnungsverarbeitung aufgebaut sind, die wir mit anderen Tieren teilen. Dies umfasst defensive Verhaltensweisen (Bedrohungsverarbeitung und Lernen, Berührung als Puffer) oder Verhaltensweisen und Fähigkeiten die zur Bindung beitragen (Belohnungsverarbeitung, Empathie, Berührung). Die hier vorliegende Doktorarbeit untersucht darum, wie affektive Verhaltensmechanismen und neurobiologische Faktoren zu sozial-emotionalen Verhaltensweisen beitragen, die Motive der Bindung und des Selbstschutzes unterstützen.

Überblick über diese Arbeit

Die vorliegende Doktorarbeit beginnt mit einem theoretischen Stück, gefolgt von drei experimentellen Berichten. In dem theoretischen Stück in Kapitel 2 stelle ich ein „Mu-Opioid-Feedback-Modell des Sozialverhaltens" vor. Das Kapitel beginnt mit einer Übersicht der aktuellen Literatur, gefolgt von einer theoretische Perspektive über die Rolle des endogenen MOR Systems im sozial-emotionalen Verhalten. Das Modell erörtert, dass das MOR-System durch seine Schlüsselfunktion in der hedonischen Wertzuweisung von positiven und negativen sozialen Reizen, auch Verhalten mit Bindungs- oder Schutzfunktion reguliert, mit langfristigen Konsequenzen für das Sozialverhalten und die psychische Gesundheit.

Kapitel 3 befasst sich mit der Frage, ob die pharmakologische Blockierung des MOR-Systems mit Naltrexon die Imitation emotionaler Gesichtsausdrücke unterbricht. Imitation emotionaler Gesichtsausdrücke ist ein automatisiertes Verhalten, welches Bindung und soziale Zusammengehörigkeit unterstützt (wenn uns z.B. jemand freundlich anlächelt tendieren wir dazu automatisch zurück zu lächeln). Diese automatische Reaktion der Gesichtsmuskeln wurde mit Elektromyographie (EMG) in einer doppelblinden, placebo-kontrollierten Studie gemessen, in der die Teilnehmer entweder Naltrexon oder Placebo erhielten. Da endogene Opioide das subjektive Gefühl von Freude an sozialer Interaktion, sowie das Gefühl der Zusammengehörigkeit, vermitteln, schlagen wir vor, dass das MOR-System auch die damit verbundenen automatischen Verhaltensweisen reguliert.

Oxytocin spielt eine entscheidende Rolle in der Wahrnehmung sozialer Signale von Kindern und damit auch in deren Entwicklung und Bindung zu den Eltern. Die Forschung legt nahe, dass aversive oder gar traumatische Erfahrungen in der Kindheit zu lang anhaltenden Veränderungen in der neuronalen, endokrinologischen und sozialen Entwicklung führen können, welche

dann die Effekte von Oxytocin verändern. In Kapitel 4 untersuchten wir darum zum einen Veränderungen in der neuronalen Sensitivität gegenüber belohnenden Signalen von Kindern durch Oxytocin, und zum anderen den Effekt von Oxytocin auf neuronale und subjektive Marker affektiver Empathie gegenüber Kindern in Notsituationen. Wir verabreichten Oxytocin oder Placebo an zwei unterschiedlichen Tagen in einer doppelblinden, funktionellen magnetresonanztomographie (fMRT) Studie. Des weiteren untersuchten wir, ob individuelle Merkmale wie negative Erfahrungen in der Kindheit der Probanden oder deren persönliche Motivation zur Fürsorge von Kindern, Auswirkungen auf die Effekte von Oxytocin hatten.

Das letzte experimentelle Kapitel, Kapitel 5, beschreibt eine Studie in der wir die Auswirkungen sozialer Berührungen auf das Blickverhalten zu unterschwellig präsentierten emotionalen Bildern untersucht haben. Die Geschwindigkeit mit der eine Person Augenkontakt von den präsentierten Gesichtern vermeidet ist ein impliziter Marker für sozial dominantes oder zurückhaltendes Verhalten. In früheren Studien zeigten wir, dass Probanden mit dominanten Persönlichkeitsmerkmalen und geringer Tendenz zu sozialer Angst, ihren Augenkontakt langsamer von Gesichtern mit konfrontativem Blick abwenden. In dieser Studie erforschen wir darum mit Infrarot Eye-Tracking die Auswirkung von Berührungen auf das Blickverhalten zu verschiedenen emotionalen Stimuli. Wie bereits vorher beschrieben können Berührungen als eine Art Puffer vor Stress schützen, was uns annehmen lässt, dass Berührungen implizit die Tendenz unterstützen sich auf soziale Herausforderungen einzulassen (und daher mehr dominante Verhaltensmermale hervorbringen).

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Curriculum Vitae and personal statement

I was born on the 22nd of January 1989 in Ottweiler, Germany. I feel lucky to be able to say that growing up, my family always supported me in the pursuit of my interests and ideas, right from the start. In school I had a strong interest in studying Biology, but quickly realized that it was human biology and behavior I was most fascinated by. My family helped me to explore different options of what I could study or work in and I found out about the field of Neuropsychology – an opportunity for me to pursue both the psychology of human behavior and the biology related to it. I decided to do a BSc in Psychology at the University of Luxemburg which I finished in 2012 with a thesis on pain processing supervised by Fernand Anton. Not only had I started to develop a passion for science during my BSc, but I also knew that I wanted to further investigate the topic of pain processing and the clinical complexity of it. Therefore, in the year following my BSc, when I was meandering through South America, I took the opportunity of doing an internship with chronic pain patients at the Universidad de los Andes in Bogotá, Colombia. After spending an incredibly interesting year in South America, I moved to Utrecht where I completed my MSc in Neuroscience and Cognition in 2015. The two research internships that I completed in the course of my master's degree, involving pain processing, social neuroscience and psychopharmacology, allowed me to further understand which direction I wanted to pursue in the future – investigating the underlying neurobiology of social behaviors and emotions. End of 2015 I started a PhD with Jack van Honk and Chris Dijkerman as my mentors. I gained experience and knowledge in the social neurosciences, experimental psychology and psychopharmacological research, and I had the amazing opportunity to conduct several months of research in Cape Town, South Africa. I submitted my PhD thesis in February 2020, which leads me to the here and now. I am currently living in Oslo, Norway, working as a postdoctoral researcher at Oslo University Hospital, where I investigate the role of psychosocial risk factors (e.g. history of trauma, experience of stress, drug liking) and associated biological markers in the development of opioid misuse in surgery patients. Further, I am developing my own research projects on the role of endogenous opioids in human social functioning with the support and guidance of Siri Leknes.

Publications

Peer reviewed publications

Meier, I.M., Bos, P.A., Hamilton, K., Stein, D.J., van Honk, J., Malcolm-Smith, S., 2016. Naltrexone increases negatively-valenced facial responses to happy faces in female participants. Psychoneuroendocrinology 74, 65–68. https://doi.org/10.1016/j.psyneuen.2016.08.022.

Preprints

Meier, I.M., van Honk, J., Bos, P.A., Terburg, D. (2020). Social touch increases dominant gaze in social confrontations. Preprint PsyArXiv. https://doi.org/10.31234/osf.io/ubyv3. Submitted.

Meier, I.M., van Honk, J., Bos, P.A., Terburg, D. (2020). A mu-opioid feedback model of human social behavior. Preprint PsyArXiv. https://doi.org/10.31234/osf.io/mhjyw. Submitted.

In preparation

Meier, I.M., Montoya, E., Spencer, H., Orellana, S., van Honk, J., Bos, P.A., Oxytocin increases reactivity in the amygdala and hippocampus to emotional stimuli of children in women depending on childhood emotional neglect.

Conference output

Oral presentations

Meier, I.M., Bos, P.A., Hamilton, K., Stein, D.J., van Honk, J., Malcolm-Smith, S. (2018). Naltrexone increases negatively-valenced facial responses to happy faces in female participants. Consortium of European Research on Emotion, Glasgow (UK).

Meier, I.M., Bos, P.A., Hamilton, K., Stein, D.J., van Honk, J., Malcolm-Smith, S. (2016). Naltrexone increases negatively-valenced facial responses to happy faces in female participants. Oral presentation at the Helmholtz Retreat, Schoorl (NL)

Posters

Meier, I.M., Montoya, E., Spencer, H., Orellana, S., van Honk, J., Bos, P.A. (2019). Oxytocin increases reactivity in the amygdala and hippocampus to emotional stimuli of children in women depending on childhood emotional neglect. Poster presentation at the meeting of the European Behavioral Pharmacology Society, Braga (PT).