# Central modulation of affective touch, pain, and emotion in humans

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## ABSTRACT

Hedonic feelings – pleasure and displeasure – strongly motivate human behavior. When well-functioning, hedonic feelings guide adaptive decision-making that promotes survival and well-being. Specialized afferent systems transmit information about the environment that gives rise to somatic pleasure or pain. However, these feelings are also influenced by expectations, learning, and information from other sensory modalities. This thesis investigates how hedonic somatic sensations are shaped by expectations and socially relevant information from other senses in healthy humans. Moreover, we assess the neurobiological systems involved in modulation of hedonic feelings. For instance, we examine the role of the neuropeptide oxytocin in the interplay between visual information of facial emotional expressions and gentle inter-personal touch, which characterizes a range of social encounters.

To navigate in the social world, humans combine available sensory information, such as facial emotional expressions and gentle affective touch. The neuropeptide oxytocin plays an important role in social bond formation, and is thought to be central in affective touch signaling. Using intranasal oxytocin and a crossover design, we assessed the role of this neuropeptide in the interaction between socially relevant tactile and visual information (**Paper I**). After intranasal oxytocin treatment, gentle inter-personal touch sharpened social impressions of concomitantly presented facial expressions, making smiling faces appear more friendly and attractive, but frowning faces less friendly and attractive. Correspondingly, gentle human touch was rated as most pleasant when paired with a smiling face, but least pleasant when combined with a frowning face. We found no evidence that oxytocin modulated touch perception. Further, we investigated oxytocin effects on sensitivity to others' explicit and implicit (hidden) emotional expressions (**Paper II**). We found that oxytocin intensified evaluations of explicitly and implicitly expressed emotions, in both angry and happy faces. This was underpinned by oxytocin-induced increase in stimulus-related pupil dilation,

which we interpret as an indication of increased attention to these socially relevant stimuli.

The malleability of hedonic feelings is illustrated by placebo effects, whereby the meaning of a medical treatment can provide significant symptom improvement, even when the treatment itself does not contain any ingredients that affect symptomatology. We compared the brain processing involved in placebo improvement of positive (pleasant touch) and negative (pain) hedonic feelings, using functional magnetic resonance imaging (**Paper III**). Placebo-induced increase in touch pleasantness (hyperhedonia) was underpinned by increased sensory processing, while decrease in pain (analgesia) was underpinned by suppression of sensory processing. Moreover, both placebo hyperhedonia and analgesia were associated with activation of similar circuitry implicated in emotion and valuation. The close correspondence of placebo hyperhedonia and analgesia might reflect an underlying shared mechanism. Recent theorizing suggests that placebo effects may build on a generalized mechanism of reward prediction. In **Paper IV,** we investigated whether expectation of *either* hyperhedonia *or* analgesia alone, would be enough to improve *both* positive and negative hedonic feelings. Participants were divided into two groups. One viewed a video documentary designed to induce expectation of hyperhedonia only, whereas the other group was led to expect analgesia after a (placebo) treatment. Both groups showed robust placebo hyperhedonia and analgesia, and the magnitudes of these effects were comparable across groups.

The work in this thesis sheds light on how expectations and available cross-sensory information shape hedonic somatic feelings, and how this impacts on social evaluation of others. These findings may contribute to the understanding of how expectations, motivations, and the quality of the patient-clinician encounter impact on hedonic sensations and, in turn, treatment outcome.

**Keywords**: Hedonic, touch, pleasure, pain, placebo effect, emotional expressions, oxytocin, fMRI, psychophysics, pupillometry

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# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Ellingsen DM**, Wessberg J, Chelnokova O, Olausson H, Laeng B, Leknes S. In touch with your emotions: Oxytocin and touch change social impressions while others' facial expressions can alter touch.
*Psychoneuroendocrinology* 2014; 39: 11-20.

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

III. **Ellingsen DM**, Wessberg J, Eikemo M, Liljencrantz J, Endestad T, Olausson H, Leknes S. Placebo improves pleasure and pain through opposite modulation of sensory processing.
*Proceedings of the National Academy of Sciences of the United States of America* 2013; 110: 17993-17998.

IV. **Ellingsen DM**, Leknes S, Triscoli C, Olausson H, Wessberg J. Expectation of either analgesia or hyperhedonia leads to both.
*Manuscript.*

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# ABBREVIATIONS

| | |
|---|---|
| ANA | Analgesia suggestion |
| ACC | Anterior cingulate cortex |
| AVP | Arginine Vasopressin |
| BBB | Blood-brain barrier |
| BOLD | Blood-oxygen level-dependent |
| CSF | Cerebrospinal fluid |
| CT | Unmyelinated low-threshold mechanoreceptor |
| fMRI | Functional magnetic resonance imaging |
| HYP | Hyperhedonia suggestion |
| LC | Locus Coeruleus |
| NAc | Nucleus accumbens |
| OFC | Orbitofrontal cortex |
| PAG | Periaqueductal gray |
| pINS | Posterior insula |
| RVM | Rostroventral medulla |
| SI | Primary somatosensory area |
| SII | Secondary somatosensory area |
| VAS | Visual analogue scale |
| vmPFC | Ventromedial prefrontal cortex |
| VTA | Ventral tegmental area |

# 1 INTRODUCTION

Hedonic feelings – pleasure and displeasure – are at the heart of human lives. While much of our behavior is geared towards seeking pleasant experiences over both the short and long run, we will also work to avoid aversive or painful experiences. The hedonic valuation of sensation helps guide us towards which behaviors to engage in and which behaviors to avoid, thus rendering hedonic processing essential for survival of both the individual and the species. Indeed, the neurobiological systems implicated in hedonic processing are central to functioning that is fundamental for survival and the maintenance of well-being, e.g. defense, maintenance of energy and nutritional supplies, fluid balance, thermoregulation, and reproduction (LeDoux, 2012, Richard et al., 2013). Pleasure or displeasure are rarely standalone sensations in their own right – they are usually "about" something – and can be conceptualized as the "hedonic gloss" that is painted onto sensations (Frijda, 2010, Kringelbach, 2010, Kringelbach and Berridge, 2010). Adaptive behavior can be completely different depending on, for example, the context and concurrent homeostatic state, and the hedonic value of a stimulus is consequently malleable. While the taste of chocolate can evoke intense feelings of pleasure, the very same stimulus can change its value and become less pleasurable after having eaten too much (Small et al., 2001). Similarly, the same sensual caress can be enchanting or repulsive, depending on the perceived identity of the toucher (Gazzola et al., 2012). This thesis investigates how hedonic somatic sensations are shaped by expectations (**Paper III and IV**) and socially relevant information from other senses (**Paper I**). Moreover, we probe the role of the neuropeptide oxytocin in the interplay between visual information of facial emotional expressions (**Paper II**) and gentle inter-personal touch (**Paper I**), which characterizes a range of social encounters.

## 1.1 Hedonic value of touch

Somatic sensations from the skin often signal that something is in physical contact with our body. Being able to quickly identify what this is, and to determine whether it is a welcome stimulus or a (potential) threat to our health is crucial for survival and well-being. Pain, for example, warns us of potential and/or actual tissue damage, which may call for immediate action to withdraw from or remove the painful stimulus.

We are equipped with a somatosensory afferent system that accurately informs us about the physical characteristics of our environment. Such sensory-discriminative signals are transmitted through myelinated low-threshold mechanoreceptive (Aβ) afferents (Abraira and Ginty, 2013). While we use our skin to explore our immediate environment, we also use it to communicate with others. Although the communicative and affective roles of touch are less studied than the more sensory-discriminative aspects, this has lately received increased attention (Hertenstein et al., 2009, Morrison et al., 2010). Infant-parent touch has important consequences for development (Hertenstein and Campos, 2001, Muir, 2002, Fairhurst et al., 2014, McGlone et al., in press), and the quantity and quality of touch observed between romantic couples has been reported to closely reflect self-reported intimacy and happiness of their relationships (Beier and Sternberg, 1977, Heslin and Boss, 1980).

Lately, an afferent system of unmyelinated mechanoreceptive afferents with very low thresholds (C-tactile, or CT) has been explored in humans (Nordin, 1990, Vallbo et al., 1993, Vallbo et al., 1999, Wessberg et al., 2003). These afferents respond vigorously to caress-like slowly stroking touch, preferably delivered at skin temperature (32°C) (Ackerley et al., 2014), and their firing correlates with pleasantness ratings. Their response properties are therefore different than the myelinated (Aβ) fibers, which are better suited for coding discriminatory tactile information (Löken et al., 2009). Functional magnetic resonance imaging (fMRI) studies in patients with selective loss of myelinated (Aβ) afferents, but with intact CT function, show that CT-mediated light touch elicits activation of the posterior insular cortex (Olausson et al., 2002, Bjornsdotter et al., 2009). Moreover, the patients report a weak and poorly localized sensation of pleasant touch to this stimulation (Olausson et al., 2008). Thus, evidence suggest that CTs play a fundamental role in providing information about the *pleasantness* of touch, with implications for affiliative behavior (McGlone et al., in press).

## 1.2 Consequences of affective touch

Being touched by another human being can evoke powerful emotions. People are remarkably accurate in detecting a wide range of emotional messages, even when these are communicated exclusively through touch (Hertenstein et al., 2006a). Positive consequences of interpersonal touch on social behavior have been demonstrated by a range of naturalistic studies. In one study, restaurant diners tipped more if the waitress had casually touched them when returning their change (Crusco and Wetzel, 1984). In another study, people

were more satisfied with a library visit if the librarian had casually touched their hand (Fisher et al., 1976). Similar studies report that when casually touched, people are more likely to return money left in a public phone (Kleinke, 1977), spend money in a shop (Hornik, 1992), or give away cigarettes (Joule and Gueguen, 2007). In most such studies however, touch formed part of an affectively congruent situation. Less is known about the effects and appraisal of touch in contexts where other available information is affectively incongruent, such as being casually touched by someone expressing anger. Appraisal of social situations relies on a combination of all available information from the senses, along with prior knowledge and expectations. According to the feelings-as-information view, affective information is also a powerful factor in appraisal of social and non-social situations, even when the affect is elicited by unrelated or incongruent events (Schwarz and Clore, 1983, 2007). For instance, one study showed that subliminally priming participants with smiling faces made them drink more fruit juice, compared to people primed with frowning faces (Winkielman et al., 2005). **Paper I** investigates how human gentle touch influences impressions of others with positive (smiling) or negative (frowning) emotional expressions, and in turn, how others' emotional expressions affects hedonic touch experience.

## 1.3 Oxytocin – the social peptide

The neuropeptide oxytocin plays an important role in a range of emotional and social behavior in humans and animals (Campbell, 2008, Bartz et al., 2011, Olff et al., 2013). An extensive body of animal research underlines the importance of oxytocin for establishing and maintaining social bonds (Feldman, 2012). Evidence from research in humans and rodents suggest that oxytocin may promote approach behavior through selective increases in parasympathetic activity (Gamer and Buchel, 2012, Kemp et al., 2012, Quintana et al., 2013) and antinociception (Uvnas-Moberg et al., 1993, Yang, 1994, Petersson et al., 1996, Lund et al., 2002), and thereby foster social affiliation. Oxytocin has been proposed to play a key role in social grooming behavior in nonhuman primates (Pedersen et al., 1988, Francis et al., 2000), and peripheral oxytocin release has been observed in response to stroking touch in dogs and rodents (Lund et al., 2002, Odendaal and Meintjes, 2003). Human studies have reported that a high frequency of physical contact with a partner predicts elevated oxytocin plasma levels (Light et al., 2005). Moreover, people given a massage are more trusting in a subsequent social interaction (trust game), an effect that covaries with plasma oxytocin levels (Morhenn et al., 2012). Furthermore, peripheral levels of oxytocin are

positively associated with parental touch of infants. Specifically, high plasma oxytocin predicts affectionate touch in mothers, and stimulatory touch in fathers (Feldman, 2012). Although these studies suggest an involvement of oxytocin in affiliative touch, its specific role in humans is far from clear. Some studies have found peripheral oxytocin release in response to touch (Light et al., 2000, Odendaal and Meintjes, 2003, Light et al., 2005, Holt-Lunstad et al., 2008), while others have found no effect (Turner et al., 1999, Heinrichs et al., 2001, Wikstrom et al., 2003, Grewen et al., 2005, Ditzen et al., 2007). These apparent discrepancies may reflect important influences of context and individual differences (Bartz et al., 2011). For example in rats, oxytocin is involved in both affiliative and aggressive approach behavior, depending on the context (Campbell, 2008). The appraised meaning of touch is likely derived largely from other sensory signals, such as visual information of the toucher's face or the tone of her/his voice. Consequently, adaptive responses should be dramatically different depending on whether the toucher appears friendly or threatening. In **Paper I** we investigated the reciprocal influence of gentle human touch and happy/frowning faces on the evaluation of these stimuli, and assessed the role of oxytocin in these interactions.

In recent years, oxytocin's role in social cognition and behavior has been assessed in experimental studies in humans, mostly through the use of an intranasal oxytocin agonist. Early studies reported advantageous "prosocial" effects of intranasal oxytocin on increasing trust (Kosfeld et al., 2005), generosity (Zak et al., 2007), and positive communication during conflicts (Ditzen et al., 2009), and decreasing social stress and anxiety (Heinrichs et al., 2003). However, when later studies employed experimental designs that better allowed for the assessment of less virtuous emotions or attitudes, intranasal oxytocin reportedly increased feelings of envy and schadenfreude (Shamay-Tsoory et al., 2009), in-group conformity (Stallen et al., 2012) and aggression towards strangers in out-groups (De Dreu et al., 2011, Shalvi and De Dreu, 2014). A recent study even reported that oxytocin *increased* anxiety during a psychotherapy session with males suffering from major depression, contrary to the reported anxiolytic effects of oxytocin (MacDonald et al., 2013).

With observations that oxytocin increased social attention (Ellenbogen et al., 2012, Gamer and Buchel, 2012), gaze to the eye region of pictures of faces, and the ability to ''read'' others emotions (Domes et al., 2007, Bartz et al., 2010, Van IJzendoorn and Bakermans-Kranenburg, 2012), a more nuanced picture emerged, suggesting that oxytocin mediates the salience of socially relevant cues more broadly (Shamay-Tsoory et al., 2009), potentially

reflecting a role of oxytocin in promoting approach-related social behavior, while inhibiting withdrawal-related behavior potentially through promoting social approach (Kemp and Guastella, 2010, 2011). This is consistent with the often dramatic effects of oxytocin in non-human animals (Insel and Young, 2001, Campbell, 2008). For instance, oxytocin enhances nurturing and reduces maternal aggression towards rat pups. At the same time, it also enhances maternal aggression towards potential threats (Insel and Young, 2001, Campbell, 2008). In **Paper II** we investigated the role of oxytocin in the evaluation of two facial expressions related to prosocial and aggressive behavior in humans, happiness and anger. Further, we investigated how oxytocin influenced the sensitivity to these expressions when these emotional cues were displayed too subtly to be explicitly recognized (Laeng et al., 2010). The effect of oxytocin on emotion recognition is often subject to individual variability, and some studies suggest that oxytocin processing is disrupted in psychiatric disorders characterized by deficits in emotional and social functioning such as autism spectrum disorders (Insel et al., 1999, Wu et al., 2005, Jacob et al., 2007, Rodrigues et al., 2009, but see Tansey et al., 2010). When assessing emotions recognition in images of eyes expressing complex emotions such as amusement or skepticism, oxytocin's enhancement of task performance has been reported for both more difficult (Domes et al., 2007) and 'easy' items (Guastella et al., 2010). Interestingly, since the study populations differed in social competence, the 'easy' items in the study by Guastella et al. and the 'difficult' items used by Domes et al. may have represented a comparable challenge to their respective study populations (high-functioning autists vs. healthy volunteers). Moreover, Bartz et al. (2010) demonstrated that oxytocin's effects on empathic accuracy in healthy males were proportional to their level of autistic traits, as assessed by the Autism Spectrum Quotient (AQ). In **Paper II**, we investigated, in a group of healthy volunteers, whether the influence of oxytocin on the appraisal of subtle expressions of happiness and anger depended on their ability to detect these emotional cues at baseline.

## 1.4 The hedonic brain

How are hedonic feelings of pleasure and aversion created in the brain? For many years, the mesolimbic dopaminergic system, consisting of the ventral tegmentum, amygdala, and ventral striatum, was assumed to be responsible for pleasure processing (Salamone and Correa, 2012). This idea grew from observations that rodents with microelectrode implants in mesolimbic locations (e.g. nucleus accumbens, NAc) would self-stimulate to obtain electrical stimulation from the microelectrode (Olds and Milner, 1954,

Valenstein et al., 1970, Shizgal et al., 2001). When given the ability to turn on the current themselves by pulling a lever, they would obsessively pull the lever – sometimes up to 2000 times per hour (Olds, 1956). Some similar experiments were even performed in human patients with mental illnesses. These patients engaged in "lever pressing", sometimes obsessively, which released electrical pulses from electrode implants in various mesolimbic locations (Heath, 1972, Portenoy et al., 1986). However, it is not clear whether they actually enjoyed these pulses, or if their behavior involved excessive wanting without much liking (Berridge and Kringelbach, 2008, Green et al., 2010, Smith, 2010, Kringelbach and Berridge, 2012).

The blockade of dopaminergic signaling typically disrupts reward-directed and consummatory behaviors in rodents (Berridge and Robinson, 1998, Schultz, 2002). Extensive destruction of dopaminergic neurons can completely abolish a rat's interest in food, to the extent that they will starve to death unless artificially fed (Berridge and Robinson, 1998). In humans, a wide range of reward-related activities has been associated with dopamine signaling (Egerton et al., 2009), e.g. anticipation and emotional reactions to pleasurable music, presentation of cocaine, drug-associated stimuli, video games, and monetary rewards (Breiter et al., 1997, Volkow et al., 1997, Koepp et al., 1998, Scott et al., 2007, Salimpoor et al., 2011)

These findings lead to the widespread idea of dopamine as a "common neural currency" for pleasant rewards (Schultz, 2002). However, while manipulations of dopaminergic signaling or microinjections of dopamine into different parts of this "reward network" often increase how much the animal would work to obtain a reward ('wanting'), it does little to change the hedonic impact of the reward – i.e. how much an animal lick its lips when consuming the sucrose ('liking'). In contrast, microinjections of opioids (and certain other neurochemicals) into discrete locations in ventral pallidum and the rostral part of the NAc enhance the intensity of actual 'liking' (Pecina and Berridge, 2005). The "hedonic hotspots", where microinjections of opioids increase 'liking' are very small in size compared to locations where opioid or dopamine microinjections increase 'wanting' responses. The hotspots correspond to <10% of the accumbens shell (about 1 $mm^3$ in rodents and 10 $mm^3$ in humans, if proportional) and the ventral pallidum.

Apart from the circuitry that has been found to cause pleasure in animal experiments, there are a number of cortical and subcortical regions that are implicated in the processing of pleasure. Functional neuroimaging in humans suggest that orbitofrontal, insular and ventromedial prefrontal cortices (vmPFC), as well as the amygdala, periaqueductal grey (PAG), and ventral

tegmental area (VTA), play important roles in reward processing. Activity in this circuitry often correlates with self-reported pleasure (Rolls et al., 2003, Kringelbach, 2005, Grabenhorst et al., 2008). The vmPFC constitute a set of interconnected regions that may integrate information from episodic memory, sensory events, social cognition and current bodily state to construct affective meaning (Roy et al., 2012) It has reciprocal projections to numerous cortical, limbic and midbrain structures, and is a central node in the resting default network (Gusnard et al., 2001, Greicius et al., 2003). Moreover, as we will see below, the vmPFC and anterior cingulate cortex (ACC) play important roles in placebo responses.

Although these cortical regions appear to code hedonic value, it is possible that these regions are not necessary for experiencing pleasure. Thousands of human patients received prefrontal lobotomy in the 1950s with massive damage to the ACC and OFC. However, in spite of clear deficits in decision making and dramatic personality changes, these patients did not seem to lose the capacity for hedonic feelings, and continued to live affective lives (Valenstein, 1986, Damasio, 2000). Further, case reports suggest that capacity for basic affective responses, such as expressions of food liking, may be relatively intact in patients with insular or prefrontal damage (Shewmon et al., 1999, Starr et al., 2009, Damasio et al., 2012). Together, these cases suggest that although playing important roles in the hedonic valuation, cortical nodes of hedonic processing are not necessary for hedonic experience.

Pleasure and pain are often regarded as opposites – while pleasure is something we actively seek, pain is usually something we work to avoid. Physical pain is a multifaceted phenomenon, involving sensory-discriminative aspects, motor responses, motivational processes and attention. Nevertheless, the hedonic displeasure, the suffering, is what often comes to mind when thinking about pain. This is reflected by the definition of pain by the International Society for the Study of Pain (IASP) – "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Merksey and Bogduk, 1994)

Human fMRI studies of pain report activations of a range of brain regions in response to experimental pain stimuli, including the thalamus, primary and secondary somatosensory areas, insula, dorsal ACC, prefrontal cortex, amygdala and brainstem structures (Tracey and Mantyh, 2007). Some functional neuroimaging studies have reported a segregation of brain systems that process the affective or hedonic aspects of physical pain and those that

process the sensory-discriminatory aspects (Rainville et al., 1997, Kulkarni et al., 2005, Auvray et al., 2010). Importantly, while these structures all play important roles in pain processing, they are not specific to pain, but are also involved in other processing, e.g. non-painful sensations (Mouraux et al., 2011, Iannetti et al., 2013). Nevertheless, by using information in fine-grained spatio-temporal patterns of fMRI activations within this "pain-responsive" circuitry, recent endeavors have been able to accurately differentiate processing of painful versus non-painful stimuli (Liang et al., 2013, Wager et al., 2013).

Are there "hot-spots" for pain, similar to those of pleasant stimuli? In rodents, AMPA-blocking or GABA-stimulating microinjection within the NAc shell can produce a range of positive and negative affective responses depending on location, resembling an "affective keyboard" (Berridge and Kringelbach, 2013). While microinjections in rostral locations generate eating responses in the animals, injections of the same drug in more caudal locations instead induces displays of disgust or fearful behavior (Richard et al., 2013). A similar negative-to-positive affective "gradient" has been suggested for the orbitofrontal cortex, along the medio-lateral axis, based on human fMRI studies reporting representations of positive hedonic feelings more medially and negative hedonics more laterally (Kringelbach, 2005). While these studies do not address pain specifically, the findings may point more generally to how core pleasure and displeasure are generated, which may have implications for the unpleasantness, or suffering, aspect of pain. It is therefore interesting to note the extensive spatial overlap in brain areas that process pain and reward/pleasure in humans and animals, especially in the OFC, vmPFC, NAc, ventral pallidum, and amygdala (Leknes and Tracey, 2008).

## 1.5 Subjective utility and hedonic value

While sensory afferent systems transmit crucial "bottom-up" information that gives rise to affective sensations, the hedonic impact is almost always shaped by top-down factors. Mood, attention, expectations, concurrent information from other senses, previous experience, and concurrent motivational state are examples of factors that influence the hedonic value of a stimulus. A common denominator in these influences is that the subjective utility, or concurrent usefulness, of a stimulus dictates its hedonic value (i.e. pleasantness or unpleasantness), rather that the inherent properties of the stimulus (Cabanac, 1971, Leknes and Tracey, 2008). Even stimuli that seem inherently positive, like sweet taste, can become hedonically "flipped".

Eating a delicious chocolate can be intensely pleasant if you are hungry for chocolate. Yet the delight turns to disgust if you keep eating it beyond satiety, although the sensory stimulus remains the same (Small et al., 2001). Similarly, while a hot bath is likely very pleasant if you just came in freezing from a winter storm, you may prefer an invigorating cold shower if you are boiling in the midst of a heat wave. Introducing the concept of alliesthesia, Cabanac (1971) postulated that stimuli which serve to move the organism towards physiological or psychological homeostasis should be perceived as pleasant, while stimuli that serve to move the organism out of homeostasis should be perceived as unpleasant or painful. For example, relief from pain is pleasant (Leknes et al., 2008, Leknes et al., 2011), and can increase the ability to enjoy other pleasures (Bastian et al., 2014). Similarly, food rewards are more pleasurable when they relieve a hunger state (Kringelbach et al., 2003). Therefore, by stimulating behavior that restores homeostatic balance, hedonic feelings are closely linked with the optimization of behavior (O'Reilly et al., 2013).

These principles have been employed to understand why pain is subject to considerable intra-individual variability across different situations. Physical pain is generally associated with displeasure and suffering, and is typically something an individual will work to avoid. The motivation-decision model of pain, as proposed by Fields (Fields, 2006, 2007), describes brain mechanisms that enhance or reduce the hedonic impact of events based on their relative importance at a given time. The model was initially put forward to explain modulation of pain, but the basic idea holds for all events that fall within a reward-punishment continuum. Fields postulates that – as a result of an unconscious decision-making process – any concurrent or impending event that is more important for the individual than a pain stimulus should suppress the hedonic impact of this pain. The event of superior importance may for instance be a greater threat or a potential reward. Likewise, anything judged as more important that an impending reward – for example a threat or a bigger reward – should suppress the hedonic impact and motivation for this reward. A central question is how the brain modulates this hedonic impact. Does it target the neural systems that generate pleasure or displeasure, e.g. hedonic hot and cold spots, or does it also modulate ascending sensory information that give rise to pleasure or displeasure? If so, at which levels does this modulation take place? Evidence from different fields indicates that top-down influences can modulate sensory signals at early stages of sensory processing. Focused auditory attention in humans can modulate signaling in the auditory sensory cortex as early as 20 ms poststimulus (Woldorff et al., 1993). Moreover, visual spatial attention can modulate pre-cortical signals in the lateral geniculate nucleus, the first relay between the retina and the cortex

(McAlonan et al., 2008). It is well-documented that ascending nociceptive neurons in the spinal dorsal horn are modulated by the brain (Wall, 1967, Woolf, 2011). The PAG in the midbrain controls incoming nociceptive signals indirectly through the rostroventral medulla (RVM) (Millan, 2002, Fields, 2004). Neurons in the RVM project to the spinal dorsal horn, with inhibitory or excitatory effects on nociceptive transmission (Urban and Gebhart, 1999, Neubert et al., 2004). The PAG receives direct input from the limbic structures amygdala and ventral striatum, and from the prefrontal cortex, constituting a pathway by which affective or cognitive information can influence ascending sensory information already at the spinal dorsal horn (Fields, 2004). There is also electrophysiological evidence in rodents that corticofugal projections, originating from the primary somatosensory area (SI), modulate innocuous touch signals in the cuneate and gracile nuclei of the dorsal column, the earliest relay stages for many low-threshold mechanoreceptive afferents (Nunez and Malmierca, 2007). Further, branches of low-threshold mechanoreceptors synapse at the segmental level in the spinal dorsal horn, but it is not known if central cognitive or affective information can alter touch processing at this level (Abraira and Ginty, 2013)

## 1.6 Modulation of pleasure and pain by contextual meaning

Hedonic experience is modulated by context, expectations, attention, arousal, and mood. A range of neuroimaging studies in humans show that such top-down modulation of hedonic sensations can alter widespread sensory processing in the brain (Small et al., 2001, Wager et al., 2004, de Araujo et al., 2005, Petrovic et al., 2005, Nitschke et al., 2006, Tracey and Mantyh, 2007, Berna et al., 2010, Knudsen et al., 2011, Woods et al., 2011, Gazzola et al., 2012, Amanzio et al., 2013).

A particularly useful experimental model for probing the psychological modulation of pain, but also hedonic value in general, is placebo responses. The term “placebo” is derived from the Latin stem “placebit” (“it will please”), and placebo responses refer to positive treatment outcomes that are not caused by the physical properties of the treatment, but by the meaning ascribed to it. When people expect a placebo treatment to have analgesic effects, they often report reduced pain, which is accompanied by widespread reductions of somatosensory (pain) processing in thalamus, insula, primary and secondary somatosensory areas, and dorsal ACC (Eippert et al., 2009a, Lu et al., 2010, Amanzio et al., 2013). Moreover, recent studies indicate that the expectation of treatment-induced pain relief, or pain worsening, can alter

incoming nociceptive signals in the spinal cord (Matre et al., 2006, Eippert et al., 2009b, Geuter and Buchel, 2013), consistent with the idea that cognition and expectation can activate the descending pain modulatory circuit (Fields, 2004, Eippert et al., 2009a). These placebo and nocebo studies indicate that psychological processes, in this case the expectation of treatment benefit, are able to modulate sensory information along the entire sensory neural "axis" stretching from coupling stations in the spinal dorsal horn to sensory circuitry in the brain, resulting in a reduced or amplified pain experience, respectively. Such modulation is somewhat less studied for non-nociceptive sensory processing or positive hedonic experiences. If boosting the pleasure of a pleasant sensation (hyperhedonia) works in a corresponding manner, we would expect the sensory activity of this appetitive stimulus instead to be increased. Several human neuroimaging studies have investigated expectancy- or satiety-induced changes in taste pleasantness. Most of these studies find that changes in pleasantness are underpinned by altered orbitofrontal activation (O'Doherty et al., 2000, Kringelbach et al., 2003, Grabenhorst et al., 2008, Plassmann et al., 2008), and some also find modulation of the primary gustatory cortex in the mid-insula (Nitschke et al., 2006, Woods et al., 2011). In **Paper III**, we compared the brain processing mediating the placebo improvement of negative (pain) and positive (pleasant touch) hedonic somatic sensations, using functional MRI. Specifically, we investigated whether placebo improvement of pleasant touch, like pain, is underpinned by modulation of somatosensory processing.

## 1.7 Placebo modulation of hedonic experience

Placebo analgesia, and placebo responses in general, have been theorized to build on a generalized mechanism of reward prediction, whereby brain valuation systems suppress pain signals when an impending treatment is believed to provide symptom improvement, e.g. pain relief (Fields, 2004, Petrovic et al., 2005, de la Fuente-Fernandez, 2009). This is supported by a growing literature showing the involvement of neural circuits implicated in reward and valuation processing (Scott et al., 2007, Wager et al., 2007, Scott et al., 2008, Schweinhardt et al., 2009, Amanzio et al., 2013). During placebo analgesia, activity in the ventromedial PFC, OFC, ventral striatum, amygdala and the midbrain, is increased, and is thought to be responsible for the suppression of pain. This modulatory network is dependent on opioid processing, since administration of the opioid receptor antagonist naloxone can attenuate both the reduced pain reports (Levine et al., 1978, Amanzio and Benedetti, 1999) and the reduction in somatosensory processing (Eippert et

al., 2009a). The modulatory network responsible for placebo analgesia may play a more general role in the expectancy-induced modulation of hedonic sensations. Petrovic and colleagues (2005) used a conditioning paradigm, whereby participants were shown threatening images before and after administration of the anxiolytic drug midozalam. This drug robustly reduced self-reported unpleasantness from viewing the images. In a subsequent session, participants who were given a placebo labeled as midozalam, reported reductions in unpleasantness comparable to the active substance. Furthermore, the placebo improvement was underpinned by increased fMRI activation in ventral striatum, rostral ACC and mid-lateral OFC, but suppressed visual cortex responses to the aversive images. In line with the close correspondence between processing of pleasure and pain (Leknes and Tracey, 2008, Fields, 2011), we investigated whether similar modulatory circuitry underpins expectancy-induced improvement of negative (painful) and positive (pleasant) feelings (**Paper III**).

As predicted by the motivation-decision model, motivational states modify the hedonic impact of sensory events (Fields, 2004, Fields, 2006). For example, rats that expect to receive highly palatable chocolate treats when standing on a hot plate endure twice as much pain compared to rats that expect to receive only regular laboratory food (Dum and Herz, 1984). Similarly, humans endure more experimental ischemic pain if they believe the pain stimulation has therapeutic effects (Benedetti et al., 2013). In the context of medical treatment, it is possible that the expectation of treatment-induced improvements may induce a shift in a "motivational state" that affects both negative and positive hedonic feelings (Fields, 2004, Fields, 2006). Specifically, if the importance of pain is reduced, more focus can be put on other important activities, like reward seeking. Vice versa, if the hedonic impact of a pleasant event is increased, concurrent pain signals may be rendered less important, or threatening, reminiscent of studies showing that pleasant stimuli can induce analgesia (Forsberg et al., 1987, Villemure et al., 2003, Kenntner-Mabiala and Pauli, 2005, Reboucas et al., 2005, Roy et al., 2008). We investigated whether the expectation of improvement of *either* pleasant *or* painful touch specifically modulates the targeted sensory experience (pain or pleasant touch), or if such positive expectations cause a general shift in motivational state that influences both positive and negative hedonic feelings (**Paper IV**).

# 2 SPECIFIC AIMS

Hedonic somatic feelings (e.g. pleasant touch and physical pain) serve to guide us towards adaptive behavior. While specialized afferent systems transmit information about the environment that give rise to somatic pleasure or pain, these sensations are heavily influenced by expectation, learning, and social information from other sensory modalities. The following specific questions were addressed:

**Paper I:** How does interpersonal touch alter social impressions of others, and vice versa, how does viewing others' facial expressions affect the hedonic appraisal of touch? Furthermore, is oxytocin involved in these interactions?

**Paper II:** What is the role of oxytocin in the evaluation of others' subtle and explicit emotional expressions?

**Paper III:** Does placebo improvement of pleasant touch involve up-regulation of touch signaling in central somatosensory circuitry, akin to suppression of pain signaling in placebo analgesia? Moreover, does placebo improvement of pleasure and pain rely on the activation of a common modulatory brain network?

**Paper IV:** Can the expectation of improved pleasure induce analgesia, and can the expectation of pain relief induce hyperhedonia?

# 3 METHODOLOGICAL CONSIDERATIONS

## 3.1 Ethics

The studies were approved by the regional ethics committees at the University of Oslo (**Paper I-III**) and the University of Gothenburg (**Paper III and IV**). The studies were performed in line with the declaration of Helsinki (1996), and written informed consent was obtained from all participants.

## 3.2 Participants

All participants were self-described healthy volunteers, and were recruited through advertisements (at the campuses of the University of Oslo (**Paper I-III**) and the University of Gothenburg (**Paper III and IV**). All participants received monetary reimbursement in accordance with the ethical approvals.

## 3.3 Summary of the protocols

### 3.3.1 Paper I

To investigate how oxytocin and gentle inter-individual touch affect social impressions of others, and how others' facial expressions and oxytocin affect touch experience, we conducted a placebo-controlled crossover study using intranasal oxytocin. Forty healthy volunteers viewed images of different facial expressions along with concomitant gentle human touch or control machine touch, while pupil diameter was monitored. After each stimulus pair, participants rated the perceived friendliness and attractiveness of the faces, perceived facial expression, or pleasantness and intensity of the touch. Thirty minutes before the experimental protocol, the participants self-administered either intranasal oxytocin or a saline solution.

### 3.3.2 Paper II

In this study we investigated the effects of intranasal oxytocin treatment on the evaluation of explicit and ‘hidden’ emotional facial expressions and related the results to individual differences in sensitivity to others’ subtle expressions of anger and happiness. Since **Paper I** and **Paper II** deal with

separate data derived from the same data collection, the experimental protocol was identical to that of **Paper I**.

### 3.3.3 Paper III

To compare the brain processing of placebo hyperhedonia and placebo analgesia, we conducted a crossover study using functional magnetic resonance imaging (fMRI). Thirty healthy participants received gentle brush strokes, moderately pleasant warmth stimuli, and moderately painful heat stimuli on two separate days. These stimuli were applied on the left arm for 10 seconds in a pseudorandomized order. In the placebo session, participants self-administered a saline nasal spray prior to the experimental protocol. They were informed that the nasal spray could contain oxytocin, and could thereby: i) increase the pleasantness of stroking and ii) warm touch, and iii) reduce the unpleasantness of painful touch. To strengthen the participants' expectation of the effects of the nasal spray, they were shown a short documentary summarizing scientific findings of such oxytocin effects. The control session was identical to the placebo session except that there was no nasal spray administration. Session order was counterbalanced, and the experimenter who administered the tactile stimuli was blinded to whether it was the placebo or the control session.

### 3.3.4 Paper IV

We further developed the protocol from **Paper III** to investigate whether suggestion of treatment benefit on *either* touch pleasantness *or* pain unpleasantness by itself can bring about placebo improvement of both pleasure (hyperhedonia) and pain (analgesia). Using a crossover design, 47 healthy volunteers received gentle brush strokes and moderately painful heat on two separate days. In the placebo session, participants self-administered a saline nasal spray suggested to either (1) improve the pleasantness of touch (HYP group) or (2) reduce pain unpleasantness (ANA group). Next, they rated pleasantness/unpleasantness and sensory intensity of gentle stroking touch and moderate heat pain. The control session was identical except that there was no nasal spray administration. Session order was counterbalanced, and the experimenter who administered the stimuli was blinded to whether it was the placebo or the control session.

## 3.4 Stimuli

### 3.4.1 Visual stimuli (Paper I and II)

The visual stimuli used in **Paper I and II** consisted of a total of 200 images, depicting 20 males and 20 females with the following five facial expressions: explicitly angry, implicitly angry, neutral, implicitly happy and explicitly happy. First, we chose 120 images, displaying angry, neutral and happy expressions, from the Karolinska Directed Emotional Faces database (Lundqvist et al., 1998, Calvo and Lundqvist, 2008). Then we created two implicitly emotional images of each face (happy-neutral and angry-neutral), as described by Laeng et al. (Laeng et al., 2010). Images of happy and angry faces were processed through a spatial low-pass filter, keeping only frequencies of 1-6 cycles/image. Images of neutral faces were high-pass filtered, keeping frequencies above 6 cycles/image, and overlaid onto the corresponding low-pass filtered images of angry and happy faces. One hundred unique images were presented in each session. The order of presentation was pseudo-randomized (see **Paper II**, methods, for details). Since pupil size is affected by ambient luminance, the background section of each image was altered to obtain the same net luminance. The images (11 x 11 cm) were presented on a computer monitor placed 104 cm in front of the participant, yielding a visual angle of 6°, as used in (Laeng et al., 2010).

### 3.4.2 Somatosensory stimuli

In **Paper I and II**, we investigated how interpersonal touch perception interacts with visual images of others. We therefore applied gentle touch from another human, compared to an intensity-matched vibratory control stimulus from a machine. In order to investigate placebo improvement of positive and negative hedonics, we used gentle stroking touch applied with a paintbrush (**Paper III and IV**), moderate warm touch (**Paper III**), and moderate heat pain (**Paper III and IV**).

#### Human touch and machine touch (Paper I and II)

Human touch consisted of 3 s duration soft strokes with a velocity of 5 cm/s, a stimulus known to be optimal in activating CT-afferents (Löken et al., 2009, Ackerley et al., 2014). Since C-fibers fatigue rapidly (Vallbo et al., 1999), the strokes were alternated between two parallel areas (each about 15 cm long) of the left forearm. The strokes were performed by an experimenter wearing a silk glove, which reduced friction and variability caused by changes in the temperature and moisture levels of the skin. The experimenter was seated behind a curtain, concealed from the participant's view, to avoid

distraction due to visual contact between the participant and the experimenter.

Machine touch consisted of 70 Hz vibration, with 3 s duration, which was applied with a vibratory device to the dorsum of the three successive areas of the participant's left hand. The device was handheld by the experimenter, who was in the same proximity of the participant as during human touch. Vibratory stimuli of this frequency mainly activate myelinated Aβ afferents and CT-afferents to a lesser degree (Bessou et al., 1971) Machine touch and human touch were matched on sensory intensity, as validated by subjective reports (see results). Therefore, this stimulation served as a control stimulus for the CT-activating touch, differing from the gentle stroking in social relevance and C-fiber activity. The part of the device that was in contact with the skin was covered with silk fabric.

## Stroking touch (Paper III and IV)

In **Paper III and IV**, gentle strokes were applied to the dorsum of the participant's left forearm (20 cm distance) at a velocity of ~5 cm/s, using a 7-cm-wide soft artist's goat hair brush (Morrison et al., 2011). The brush strokes were administered for 10 s in a proximal-to-distal direction (i.e. towards the hand). Similarly to the human touch stimuli (**Paper I and II**), this type of stimulation is consistently perceived as pleasant, and efficiently activates CT-afferents, which are thought to signal affective aspects of touch (Löken et al., 2009, Olausson et al., 2010).

## Warm touch (Paper III)

A soft, gel-filled heat pad (ColdHot Pack, 3M Health Care) was heated for 60 s in a microwave oven (~42.5 °C surface temperature) immediately before the experiment. The heat pad, wrapped in thin nylon cloth, was placed gently on the dorsum of the left forearm for 10 s and then removed, resembling the touch of a warm human hand. The heat pad decreased slightly in temperature from 42.5 °C at the start, to 40 °C at the end of the ~15 minutes long experiment. A comparison between stimulus ratings in the first versus the last half of the experiment showed a slight decrease in perceived pleasantness, which may be related to the decrease in temperature. Importantly however, this effect did not significantly differ between placebo and control sessions ($p = 0.2$).

## Moderate heat-pain (Paper III and IV)

Heat stimuli were delivered using an MRI compatible peltier thermode (Pathway model ATS, 30 × 30 mm, Medoc). A moderately painful temperature, which was selected for each participant before the first

experimental session (5 on a numeric rating scale, NRS, with anchors 0 = no pain; 1 = pain threshold; 10 = intense pain), was used during both experimental sessions (mean temperatures: **Paper III**: 47.1 ± 0.73°C; **Paper IV**: 47.2 ± 0.73°C). The thermode was placed on the dorsum of the participant's left hand for 10 s, and then removed. Participants were not informed that the same temperature was used for all heat stimuli, but were instructed to focus on their experience of each individual stimulus. To avoid skin sensitization that could affect the positive touch experience, painful touch was applied at a location adjacent to the pleasant touch stimuli.

## 3.5 Oxytocin administration

In **Paper I and II**, each individual participated in two sessions on separate days (on average 3.4 (SD = 3.3, range 1—15) days apart), in counterbalanced order: once with 40 International Units (IU) oxytocin (Syntocinon, Novartis, Basel, Switzerland; ten puffs alternating between the left and the right nostril) and once with saline (0.9%, Miwana, Gällivare, Sweden; ten puffs alternating as above), in a double-blind manner.

### 3.5.1 How does intranasal oxytocin affect cognition and behavior?

There is a myriad of studies showing behavioral effects of intranasal oxytocin administration. There are however many unanswered questions related to how exactly nasal oxytocin affect behavior, cognition, and in some cases, sensations: Do the molecules that are sprayed into the nasal cavity enter the brain, and if so, how? Once they have entered the brain, do they reach the appropriate receptor targets? Is it possible that nasal oxytocin does not enter the brain at all, but affects behavior indirectly through its peripheral action in (e.g. the heart or gut, where it is likely to affect afferent signaling)?

Two important human studies provide some insight into the route of intranasal oxytocin. One investigation measured ventricular spinal fluid levels of arginine vasopressin (AVP), a neuropeptide that is structurally very similar to oxytocin, after intranasal administration of 40 or 80 IU of AVP (Born et al., 2002). They found a dose-dependent increase in spinal cerebrospinal fluid (CSF) levels of AVP few minutes after administration, which lasted for at least 80 minutes. The authors suggested two possible routes whereby the neuropeptides reached the brain. One possibility involved the internalization of peptides into olfactory neurons, followed by intraneuronal axonal transport, though the authors noted that this sluggish process could potentially take hours, and therefore was unlikely to be the

cause the relatively rapid rise of AVP in CSF. Another possibility, suggested by the authors to be more likely, is an extraneuronal route whereby peptides passed through intercellular clefts in the olfactory epithelium, to then diffuse through the subarachnoid space into ventricular CSF. Importantly, this study used AVP and not oxytocin, and assessed spinal CSF levels and not binding to brain receptors. Nevertheless, due to the structural similarity between AVP and oxytocin, the study is often cited in support of the assumption that intranasal oxytocin influences behavior through direct effects in the brain. A recent study replicated this study with intranasal oxytocin. They assessed oxytocin levels in plasma and spinal CSF 0 to 75 min after intranasal oxytocin, and report an increase in oxytocin levels in both blood plasma and spinal CSF (Striepens et al., 2013). However, while the increase in plasma level was almost immediate and lasted throughout the assessment, spinal CSF levels of oxytocin (perhaps surprisingly) did not increase until 75 min after intranasal administration. Therefore, while the observation may indicate that "oxytocin reaches the brain", it remains entirely possible that this increase arises from endogenous oxytocin release, resulting from indirect central or peripheral effects of intranasal oxytocin. Furthermore, the very small sample size of this between-subjects study (CSF data 75 min after administration consisted of only one individual) warrants replication. A recent study reported increased extracellular levels of oxytocin in the amygdala and hippocampus in rodents, as early as 30 min after intranasal oxytocin administration (Neumann et al., 2013), supporting the notion that intranasal oxytocin reaches relevant limbic structures. Note that in human studies, intranasal oxytocin is typically administered about 30-45 min before testing.

Although these studies support that intranasal oxytocin may affect central targets through an intra- or extraneuronal route, this does not rule out an involvement of a peripheral "indirect" route. To what degree, if at all, oxytocin molecules can pass the blood brain barrier (BBB) is still subject to debate (McEwen, 2004, Churchland and Winkielman, 2012). Animal research indicates that the amount of plasma oxytocin that passes the BBB is only 0.01% in sheep (Kendrick et al., 1986, Kendrick et al., 1991) and 0.002% in rats (Mens et al., 1983). However, the penetrability of the BBB to oxytocin can be affected by physiological conditions, e.g. stress, hypertension and disease (Churchland and Winkielman, 2012). Nevertheless, in two studies, Hollander et al. performed intravenous infusion of oxytocin in patients with autism spectrum disorder. They report an improvement of repetitive behavior (Hollander et al., 2003) and retention of social cognition (Hollander et al., 2007) after the infusion of oxytocin relative to placebo. While this is compatible with a blood-brain route through the BBB, another possibility is binding of oxytocin to peripheral targets, e.g. afferent branches

of the vagus nerve, which are central to emotional processes. Vagal activity is closely related to the expression and regulation of emotion (Porges et al., 1994, Porges, 2007, Quintana et al., 2012), and vagal stimulation induces the release of oxytocin in the rodent brain (McEwen, 2004).

Taken together, the existing evidence suggests that intranasal oxytocin is likely to influence social behavior and cognition *both* directly via olfactory nerve pathways, *and* indirectly through the activation of afferents in the periphery and possibly via the blood stream. The labeling of intranasal oxytocin in primates or rodents, or positron emission tomography with an oxytocin receptor sensitive ligand in humans, may reveal important insights on the specific route of action.

## 3.6 Measurement and analysis

### 3.6.1 Subjective report of stimuli

Participants indicated their subjective experience of the visual and somatosensory stimuli on Visual Analog Scales (VAS) with two verbal anchors. These scales were presented on a computer monitor either immediately after (**Paper I and II**) or 8 s after (**Paper III and IV**) each stimulus.

#### Paper I and II

Ratings of three aspects of the visuo-tactile stimuli were collected: (i) perceived mood/facial expression; (ii) perception of social characteristics of the face stimuli and (iii) touch perception. Each aspect was measured via two VAS – one such rating scale pair was displayed after each stimulus in pseudo-randomized order: 1A: How happy was the person (Not happy – Happy); 1B: How angry was the person? (Not angry–Angry); 2A: How attractive was the person? (Unattractive–Attractive); 2B: How friendly was the person? (Not Friendly–Friendly); 3A: How pleasant was the touch? (Unpleasant – Pleasant) and 3B: How intense was the touch? (Not noticeable – Intense). The order of presentation of the rating scale pairs was pseudo-randomized within each session and within each rating scale pair. Therefore, the participants were unable to predict the occurrence of the specific rating scales. Participants were informed of this before the experiment onset and were instructed to pay attention to all aspects of the visual and the tactile stimuli in every trial since the subsequent rating scales could revolve around either.

### Paper III and IV

In a similar fashion, hedonic aspects (Unpleasant – Pleasant, **Paper III and IV**) and intensity aspects (Not at all intense – Very intense, **Paper IV**) of the pleasant or painful somatosensory stimuli were recorded after each stimulus. The order of presentation of the hedonic (**Paper III and IV**) and intensity scales (**Paper IV**) was pseudo-randomized.

## 3.6.2 Subjective report of mood (Paper I and IV)

In **Paper I-IV**, participants' mood was assessed by a VAS with 7 items (anchors: Not at all – Very much so), all starting with "Right now, I feel…", and ending with "frightened", "sad", "annoyed", "happy", "calm", "anxious", "alert". Mood was assessed (i) before the nasal spray administration; (ii) immediately before the experimental protocol and (iii) immediately after the experimental protocol (**Paper I-IV**).

## 3.6.3 Subjective report of treatment expectations (Paper III and IV)

After watching the video documentary about oxytocin, participants filled in a questionnaire (−3 to +3 Likert scale, with the anchors **"**completely disagree**"** and **"**completely agree**"**) addressing specific expectations about the effects of intranasal oxytocin (**Paper III and IV**). This questionnaire included 10 items, all starting with **"**I believe a nasal spray containing oxytocin will make me. . .**"** and ending either with relevant statements (experience touch as more pleasant, warmth as more pleasant (**Paper III** only), pain as less unpleasant) or with control items (feel more outgoing and social, feel less patient, discriminate better between moving touch velocities, feel touch as unpleasant, feel happier, more relaxed, feel generally more delighted). Participants filled in the same questionnaire in both sessions.

## 3.6.4 Analysis of subjective reports and questionnaires

Statistical analyses of the psychophysical data were performed using SPSS 12.0 and 18.0 (SPSS Inc., Chicago, IL, USA), and Matlab (The Mathworks Inc., Natick, MA, USA).

## 3.6.5 Functional magnetic resonance imaging (Paper III)

In order to compare brain processing involved in placebo hyperhedonia and analgesia (**Paper III**), we performed the experiments using fMRI, a

technique that utilizes a blood-oxygen level-dependent (BOLD) contrast to estimate task-related brain activity (Worsley, 2001). We used the FMRIB Software Library (FSL) for preprocessing and statistical analysis of fMRI data.

## Acquisition

Imaging was performed at the Intervention Centre, Oslo University Hospital, using a Philips Achieva 3 Tesla whole body MR unit equipped with an 8-channel Philips SENSE (reduction factor = 2) head coil (Philips Medical Systems, Best, the Netherlands). Functional images were acquired with a gradient-echo echo-planar imaging (EPI) sequence: TR = 2000 ms; TE = 30 ms; flip angle = 80°; field-of-view = 240 × 240; in-plane resolution = 3 × 3 mm; slice thickness = 3 mm; gap spacing between slices = 0.3 mm; number of axial slices (placed on the ac-pc line) = 34; number of volumes = 510. A high-resolution T1-weighted scan was acquired directly after the fMRI sequence in session two, to aid registration of the EPI images to standard space: TR = 7.1 ms; TE = 3.2 ms; flip angle = 8°; field-of-view = 256 × 256; in-plane resolution = 1 × 1 mm; slice thickness = 1 mm (no gap); number of axial slices = 160.

## Preprocessing

The following pre-statistical processing was applied within each individual run: motion correction using MCFLIRT (Jenkinson et al., 2002); non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of full-width half-maxim 5 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high pass temporal filtering (Gaussian-weighted least-squares straight line fitting with a high pass filter cutoff of 120.0 s).

We applied a denoising procedure using probabilistic independent component analysis (ICA) (Beckmann and Smith, 2004) as implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) v3.10. Independent components were visually inspected, and labeled noise-components or signal-components, following the guidelines presented by Kelly et al. (Kelly et al., 2010). The time courses of noise-components were filtered out from the preprocessed data, and the resulting denoised data were used in the statistical analyses. (See **Paper III**, Fig. S4 and Table S3 for an illustration of the effect of denoising on pain signal in the PAG/colliculi).

## Statistical Analysis

A unique input stimulus function was defined for each stimulus type (stroking, warm, and pain), and for the VAS rating intervals. Input stimulus functions were convolved with the hemodynamic response function (γHRF) to yield regressors for the GLM. Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). Registration to high-resolution structural and standard space images was carried out using FLIRT (Jenkinson and Smith, 2001, Jenkinson et al., 2002). Higher-level (group) analyses were performed using FLAME 1+2 (FMRIB's Local Analysis of Mixed Effects).

We restricted searches to regions of interest (ROI) involved in (i) somatosensory processing) and (ii) prefrontal and subcortical regions reported to mediate placebo responses, and placebo analgesia in particular. Because these regions collectively are involved in valuation and reward-related processing more generally (Lindquist et al., 2012, Roy et al., 2012), and for reasons of clarity and brevity, we will refer to this set of regions as "emotion appraisal circuitry". All a priori regions of interest (ROI) were defined from independent sources.

ROIs in contralateral parts of the somatosensory circuitry comprised: (i) posterior insula (pINS/Ig2, $p > 30\%$); (ii) primary somatosensory area (SI/area 3b, $p > 50\%$); (iii) secondary somatosensory area (SII/OP4, $p > 50\%$): Jülich histological atlas (Eickhoff et al., 2007); and (iv) sensory thalamus Oxford thalamic connectivity probability atlas ($p > 10\%$) (Behrens et al., 2003). Very few voxels are more than 50% probable of being in the pINS/Ig2 and the sensory thalamus in the Montreal Neurological Institute (MNI152) standard map. Therefore, to ensure enough space was provided for detecting effects within these structures, thresholds for these ROIs were lowered to 30% and 10%, respectively, thereby reducing the risk of type II errors (see **Paper III**, Fig. S6, for illustrations of all ROIs overlaid on a MNI152 standard brain).

ROIs defined within emotion appraisal circuitry comprised: (i) the pregenual anterior cingulate cortex (pgACC) and (ii) mOFC [spheres (8-mm radius) around peak activations from a meta-analysis of placebo analgesia (Amanzio et al., 2013)]; (iii) the nucleus accumbens (NAc) and (iv) amygdala (Harvard-Oxford subcortical atlas, P > 50%); (v) the periaqueductal gray (PAG) (mask used by Eippert et al. (2009a)); and (vi) the ventral tegmental area [VTA; manually drawn based on anatomical landmarks from the Duvernoy's Brainstem atlas (Naidich et al., 2009), ranging from MNI152 coordinates z (−10) to z (−18)]. Selection of the regions (mOFC, pgACC, PAG) for the

comparison between placebo-induced ventromedial prefrontal cortex (vmPFC)–PAG functional coupling and placebo-induced change in sensory regions was based on a priori predictions derived from this circuit's involvement in placebo analgesia (Bingel et al., 2006, Wager et al., 2007, Eippert et al., 2009a). This selection was made irrespective of these regions' activation in the basic contrast (placebo > control) because of the individual variability in placebo response magnitude.

To investigate whether structures outside the hypothesized circuitry were important for placebo hyperhedonia or analgesia, we performed voxel-based analyses using a whole-brain approach with a corrected cluster significance threshold of $p = 0.05$ (Worsley, 2001). We did not observe any additional activations that furthered our understanding of the current findings (see **Paper III**, Table S4 for the results of this analysis).

### 3.6.6 Pupillometry (Paper I and II)

#### Acquisition

The pupil diameter of the participant's left eye was measured using a non-invasive, infrared eye tracker (iView X Hi-Speed monocular system, SMI-SensoMotoric Instruments, Teltow, Germany) at a rate of 240 Hz for the duration of each stimulus pair (3000 ms).

Pupil diameter data for each participant and session were pre-processed in Matlab, and analyzed in SPSS. Because of technical constraints, (malfunction of software or hardware), some datasets were unusable. Therefore the analysis was performed with data from 25 participants (50 sessions) where we obtained good-quality recordings. Eye blinks and artifacts were excluded, leaving physiologically plausible pupil sizes of 1 - 9 mm. Average time series were created for each stimulus type; these time series were smoothed using a 10Hz cutoff low-pass filter (a five-pole Chebyshev Type II filter). The time series were normalized to reflect the total dilation of the pupil for each stimulus type by subtracting the average pupil size during the first 200 ms from all points in the time series.

#### Statistical analysis

For statistical analysis, the trimmed mean pupil dilation was computed for the ten 250-ms 'bins' between 500 and 3000 ms for each stimulus type, session and participant. The trimmed means were entered into a linear mixed model analysis using SPSS with the following variables: drug treatment (oxytocin or placebo); tactile stimulation (stroking touch or vibration) and visual facial expression (explicit anger, implicit anger, neutral, implicit happiness and

explicit happiness). A subsequent analysis further included participant gender and order of treatment presentation. In a third mixed model analysis, we also included the between-subjects variable of emotional sensitivity score, as defined from behavioral ratings.

# 3.7 Design considerations

## 3.7.1 Paper III

### Piloting and development of design

To validate that our experimental setup was able to produce the placebo responses that we aimed to investigate with fMRI, we explored various design options in a series of pilot studies with a total of ~40 healthy volunteers.

To induce an expectation of intranasal oxytocin's beneficial effects on painful and pleasant touch experience, we created a 6-min video documentary summarizing scientific findings of oxytocin's putative pro-social effects such as its involvement in bonding, love, grooming, affective touch, and healing. The video was shown to the participants before the experimental protocol in both sessions. As all of the material was based on published research, there was no deception. The video concluded that a nasal spray of oxytocin might enhance the pleasantness of: (**i**) stroking and (**ii**) warm touch, and (**iii**) reduce the unpleasantness of pain. The video was introduced using a scripted explanation: **"**Due to the recent surge in scientific and media interest in oxytocin's positive effects in humans, how much people know about oxytocin varies greatly. Thus, we show everyone this film to even out the differences.**"**

## 3.7.2 Paper IV

### Creation and validation of the documentary videos

In making the two documentary videos, we strived to make them as balanced as possible on all aspects except for their specific suggestions of hyperhedonia and analgesia. Furthermore, the information presented in both films was based on published research – thus there was no deception. The two films were narrated by the same person, who kept the same intonation. The films were comparable in duration (hyperhedonia film: 6:08 min; analgesia film: 6:15), and kept the same overall narrative structure. Finally, they involved the same net amount of depictions of social situations involving interpersonal touch (both 58 s). To formally validate the balance

and potency of the films, we presented them to 20 volunteers – 10 who viewed the hyperhedonia film and 10 who viewed the analgesia film. Before and after viewing the film, participants rated their mood (*see section 3.6.2.*). After viewing the film, they also rated their beliefs about the effects of oxytocin nasal spray (*see section 3.6.3*), and how they perceived the content and technical quality of the films. This was assessed with a 1-10 NRS with 11 items, all starting with "I found the film…", and ending with "believable", "interesting", "untrustworthy", "positive", "professional", "unpleasant", "tedious", "cozy", "negative", "emotionally charged", "amateurish".

To compare whether the two documentary films differentially impacted on the participants' (i) mood or (ii) expectations of the effects of intranasal oxytocin, and (iii) impressions of the content and technical quality of the film, we performed separate ANOVAs for each aspect.

To investigate mood responses, we performed a repeated measures ANOVA with the within-subjects factors questionnaire item and time of assessment (before the film, after the film), and the between-subjects factor video (hyperhedonia suggestion, analgesia suggestion). The results showed an expected main effect of questionnaire item ($F(2.5, 47.6) = 47.9$, $p < 0.001$), but no significant main effect of time of assessment ($F(1, 18) = 2.4$, $p = 0.14$), and no interactions involving time of assessment or video ($p$-values > 0.17). Thus, we did not find evidence that the videos, differentially or in general, influenced mood.

To investigate expectations of the effects of intranasal oxytocin, we performed a repeated measures ANOVA with the within-subjects factor questionnaire item and the between-subjects factor video (hyperhedonia expectation, analgesia expectation). The results showed an expected main effect of item ($F(4.2, 75) = 30.0$, $p < 0.001$) and a significant interaction between item and video ($F(4.2, 75) = 3.01$, $p = 0.02$). Planned paired t-tests between the response on each relevant item (touch hyperhedonia, analgesia), and the averaged responses on the irrelevant control items, were calculated within each video group. In the HYP group, expectations of touch hyperhedonia were higher than of analgesia ($p = 0.008$) and of control items ($p < 0.001$). In the ANA group, expectations of analgesia were higher than of touch hyperhedonia ($p < 0.004$) and of control items ($p < 0.001$)

To investigate participants' impressions of the content and quality of the films, we performed a repeated measures ANOVA with the within-subjects factor questionnaire item and the between-subjects factor video (hyperhedonia expectation, analgesia expectation). The results showed an

expected main effect of item ($F(4.2, 79) = 28.7$, $p < 0.001$), but there was no significant interaction between item and video ($F(4.2, 79) = 0.98$, $p = 0.42$). Thus, we did not find evidence that the two films differed in the participants' evaluations of content and technical quality.

# 4 RESULTS

## 4.1 Paper I

Here, we investigated how oxytocin and gentle human touch affect social impressions of others, and vice versa how others' facial expressions and oxytocin affect touch experience.

### 4.1.1 Oxytocin and human touch sharpened evaluations of friendliness and attractiveness

After oxytocin treatment, relative to placebo, human touch sharpened participants' social evaluation of others, such that faces with angry expressions were rated as less friendly and attractive, while faces with neutral or happy expressions were rated as more friendly and attractive.

### 4.1.2 Facial expression of others influenced pleasantness of human touch more strongly than machine touch

Ratings of pleasantness increased incrementally with the emotional valence of the concomitantly presented faces. Specifically, participants enjoyed touch the most when they were observing a smiling face, while they enjoyed touch the least when observing a frowning face. This affected the pleasantness of both human and machine touch, indicating that the effect of seeing emotional expressions is not constrained to socially relevant stimuli (e.g. touch from another human), but may work in a more unspecific fashion to impact on hedonic or affective impact in general. However, observing a frowning face had a stronger negative impact on the pleasantness of human touch compared to machine touch.

### 4.1.3 Oxytocin did not alter touch experience

Contrary to our hypothesis, intranasal administration of oxytocin affected neither touch pleasantness nor touch intensity. Although null results should always be interpreted with caution (Cumming, 2014), this may point to other neurotransmitters as responsible for shaping how touch is appraised, e.g. opioids (Løseth et al., In press). Nevertheless, in a recent study, heterosexual males reported an oxytocin-induced selective increase of self-reported pleasantness of sensual caresses only when they believed it was performed by

a woman, indicating that oxytocin's role in hedonic touch experience may depend on social context (Scheele et al., 2014).

### 4.1.4 Human touch produced larger pupil responses to happy expressions, but smaller pupil responses to angry expressions, compared to machine touch

The pupil dilates in response to rewarding and salient events, and is considered an accurate physiological index of attentional allocation (Beatty, 1982, Laeng et al., 2012). Oxytocin (relative to placebo) and human touch (relative to machine touch) independently increased pupillary responses to the visuo-tactile stimuli. Further, human touch combined with a smiling face produced the largest increase in pupil dilation while machine touch combined with a smiling face produced the smallest increase in pupil dilation.

## 4.2 Paper II

Here, we investigated the effect of oxytocin on the appraisal of others' explicit and "hidden" emotions, and assessed whether this depends on how "sensitive" people are towards others' subtle emotional expressions.

### 4.2.1 Oxytocin enhanced evaluation of explicitly and implicitly presented angry and happy facial expressions

Intranasal oxytocin induced a sharpening effect on the evaluation of presented faces. After oxytocin treatment, relative to placebo, participants rated happy faces as happier and less angry, but angry faces as angrier and less happy. This pattern was observed both for explicitly and implicitly presented facial expressions.

### 4.2.2 Sensitivity to differences in subtle expressions at baseline predicted oxytocin-enhanced emotional sensitivity

To assess whether the effect of oxytocin depended on individual differences in emotional processing, we calculated a baseline "emotional sensitivity" score for each participant. A high emotional sensitivity score was assigned to participants who expressed a large perceived difference between implicit angry and implicit happy faces (i.e. implicit angry faces as angrier and less happy than implicit happy faces). A low emotional sensitivity score was

assigned to those who expressed a small or no perceived difference between implicit angry and implicit happy faces. We investigated the association between participants' emotional sensitivity score and oxytocin's effects on task performance using linear regression analyses. Participants who perceived implicitly angry faces as angrier and less happy than implicitly happy faces without oxytocin pre-treatment showed little benefit of intranasal oxytocin. In contrast, participants who were not sensitive to the differences between the implicitly presented angry and happy expressions at baseline showed greater improvement after oxytocin treatment.

### 4.2.3 Oxytocin enhanced stimulus-induced pupil dilation

Oxytocin increased stimulus-induced pupil dilation compared to placebo, consistent with the notion that oxytocin administration increases attention towards socially relevant stimuli. We found a negative correlation between stimulus-induced pupil dilation (irrespective of oxytocin treatment) and emotional sensitivity score. Those with low emotional sensitivity had overall larger pupillary responses than those with high emotional sensitivity. This may reflect an increased attentional effort in evaluating these faces for those who showed difficulties in evaluating the implicit facial expressions. However, there was no evidence that oxytocin's beneficial effects on emotional sensitivity in this subgroup were due to additional attention to the socially relevant stimuli. Instead we found a trend towards the opposite effect, by which the high emotional sensitivity group showed a greater oxytocin enhancement of pupil dilation than did the low sensitivity group.

We also used stimulus-induced pupil dilation as an independent moderator to support the finding that oxytocin-induced sharpening depends on emotional sensitivity (see above). Indeed, we found that those with greatest task-related pupil responses at baseline, reflecting larger attentional effort, showed the greatest oxytocin-induced improvement in distinguishing implicit anger from implicit happiness.

## 4.3 Paper III

Here, we investigated the neural processing mediating expectancy-induced improvements of positive and negative hedonic feelings. We compared the placebo improvement of pleasant touch (hyperhedonia) and painful touch (analgesia), using behavioral measurements and fMRI in a crossover design.

### 4.3.1 Expectations of treatment benefit

To assess participants' expectations after viewing the documentary video suggesting beneficial effects of oxytocin, they were asked to indicate on a Likert scale how much they agreed with a set of task-relevant and control statements about effects of intranasal oxytocin. Participants reported stronger expectations of increased warm touch and stroking touch pleasantness, and reduced pain unpleasantness, compared to task-irrelevant control items.

### 4.3.2 Placebo manipulation induced hyperhedonia and analgesia

After each experimental stimulus, participants indicated on a VAS (unpleasant – pleasant) how they perceived the stimulus. Placebo treatment induced a positive shift in hedonic ratings. Specifically, participants perceived stroking touch as more pleasant, warm touch as more pleasant, and painful touch as less unpleasant, after placebo treatment compared to control. Moreover, the individual magnitude of placebo improvement (measured as the placebo-control difference in ratings) correlated positively across all three stimulus types. In other words, those who responded with strong placebo hyperhedonia also displayed strong placebo analgesia.

### 4.3.3 Opposite effects on pleasant and painful touch processing in sensory circuitry

To compare the effects of placebo hyperhedonia and analgesia on somatosensory processing, we first assessed the placebo - control difference within each stimulus modality. We found significant placebo-induced increases in BOLD responses to stroking and warm touch in the posterior insula (pINS) and secondary somatosensory area. In contrast, we found placebo-induced decreases in BOLD responses to painful touch in primary (SI) and secondary (SII) somatosensory area. Direct comparisons between stimulus types confirmed that the placebo-induced BOLD responses to stroking and warm touch differed significantly from those to painful touch in pINS, SI, and SII. There were no significant differences in the sensory thalamus.

### 4.3.4 Placebo hyperhedonia and analgesia recruited similar emotion appraisal circuitry

To investigate placebo-induced processing in emotion appraisal circuitry, we performed voxel-wise comparisons (placebo - control) within each stimulus type. We found a significant placebo-induced BOLD increase in the nucleus

accumbens (NAc) during stroking, warm and painful touch, in an overlapping area as revealed by a conjunction analysis. Further, we found significant increases in the PAG (stroking and warm touch), amygdala (warm touch) and VTA (warm and painful touch). Placebo-induced recruitment of emotion appraisal circuitry did not significantly differ between the three touch stimuli.

Since the magnitude of placebo responses is subject to individual variability, this should be reflected in central processing. We therefore identified covariance with the behavioral placebo response within emotion appraisal circuitry by adding a regressor with each subject's average placebo improvement (placebo > control) for each stimulus type to the fMRI group analysis setup (placebo > control). This correlation analysis revealed that individuals with the strongest placebo improvement also had the largest placebo-induced BOLD increase in the mOFC (stroking), pgACC (stroking, pain), NAc (stroking, warm), amygdala (warm), PAG (stroking), and VTA (stroking, warm).

### 4.3.5 Placebo Responses Correlated with Increases in Functional Connectivity Within Emotion Appraisal Circuitry

Previous studies show that placebo analgesia is underpinned by increases in functional connectivity of the pgACC and mOFC with the PAG and amygdala (Bingel et al., 2006, Eippert et al., 2009a, Wager et al., 2011). We used a psychophysiological interaction (PPI) analysis (Friston et al., 1997, O'Reilly et al., 2012) to assess whether placebo-induced functional coupling between these prefrontal regions and subcortical emotion appraisal circuitry increased in proportion to the behavioral placebo effect. We confirmed significant placebo-induced increases in the functional coupling between prefrontal and subcortical emotion appraisal regions. Specifically, the stronger the individual placebo-induced increases in functional coupling between the mOFC and the amygdala, PAG, and NAc, the larger the reported benefit of placebo treatment on stroking touch pleasantness. Similarly, individuals with the strongest increases in functional coupling between pgACC and the mOFC, amygdala, NAc, and VTA also displayed the strongest placebo analgesia responses.

### 4.3.6 Placebo-induced functional coupling correlated with opposite modulation of sensory processing during placebo hyperhedonia and analgesia

To investigate how placebo-induced functional coupling within emotion appraisal circuitry related to sensory processing, we assessed the covariance between the placebo-induced vmPFC – PAG coupling and the placebo-induced changes in sensory areas. We performed a correlation analysis between 1) each individual's placebo-induced increase in mOFC – PAG coupling, and 2) each individual's placebo-induced change in sensory areas. Placebo-induced functional coupling between mOFC and PAG correlated with placebo-induced modulation of sensory areas in opposite directions during hyperhedonia and analgesia. Specifically, individuals with strong placebo-induced increases in mOFC-PAG coupling had larger increases in SII responses to stroking touch, but larger decreases in SII responses to painful touch. Moreover, we formally tested whether these relationships differed between placebo hyperhedonia and analgesia. Direct comparisons between these correlation coefficients revealed that the correlation between placebo-induced mOFC-PAG coupling and placebo-induced change in sensory areas (SI and pINS; separate analyses) were significantly more positive during stroking touch compared to painful touch. A similar pattern was revealed for the functional coupling between pgACC and PAG. High placebo-induced pgACC–PAG coupling correlated significantly with increases in SII responses to stroking and warm touch, and decreases in SI responses to painful touch, consistent with a general pattern of modulation across sensory circuitry.

## 4.4 Paper IV

Here, we investigated whether the suggestion of treatment benefit on either touch pleasantness or pain unpleasantness by itself can bring about placebo improvement of both pleasure (hyperhedonia) and pain (analgesia). We compared self-reported improvement of pain and touch hedonics after an intranasal placebo treatment that was suggested to either improve touch pleasantness (HYP group) or provide pain relief (ANA group).

### 4.4.1 Expectation of treatment benefit

To assess participants' expectations after viewing the documentary video suggesting beneficial effects of oxytocin, they were asked to indicate on a Likert scale how much they agreed with a set of task-relevant and control

statements about the effects of intranasal oxytocin. Participants in the HYP group reported stronger expectations of increased touch pleasantness, compared to analgesia and task-irrelevant control items. Conversely, participants in the ANA group reported stronger expectations of pain relief, compared to touch hyperhedonia and task-irrelevant control items.

### 4.4.2 Suggestion of analgesia induced hyperhedonia, and vice versa

After placebo treatment, relative to a control condition without treatment, both the HYP and the ANA groups reported increased touch pleasantness and reduced pain unpleasantness. Similarly, there was a placebo-induced improvement of sensory intensity, whereby pain intensity was reduced and touch intensity was increased, in both the HYP group and the ANA group. Moreover, we did not find evidence that the magnitudes of placebo responses differed based on the specific treatment benefit (analgesia or hyperhedonia) that was presented in the video documentary, neither generally nor differentially for each stimulus.

# 5 DISCUSSION

The work presented in this thesis sheds light on the neurobiological mechanisms whereby hedonic somatic sensations are formed, and in turn affects the social evaluation of others. We found that inter-personal touch has a "sharpening" effect on social evaluation of others (**Paper I**). Oxytocin may increase sensitivity to emotional sensory cues, through increasing attention toward socially relevant stimuli (**Paper II**). Both pleasant and painful somatic sensations are shaped by expectations and beliefs. We showed that positive beliefs in a medical treatment shaped positive (pleasant touch) and negative (painful touch) sensations by modulating widespread sensory processing to match the prediction of treatment improvement (**Paper III**). This effect may stem from an expectation-induced motivational state, such that negative hedonic feelings are suppressed and positive hedonic feelings are boosted (Fields, 2004). The participants with strong hyperhedonia responses also had strong hyperhedonia responses. This corresponding pattern prevailed even when treatment was suggested to *either* reduce pain *or* increase pleasure (**Paper IV**). Participants who were informed that the treatment would provide analgesia not only perceived noxious heat stimuli as less painful, but also found the gentle touch stimuli more pleasant. Conversely, those who were informed that the treatment would provide hyperhedonia, without mention of analgesia, found the positive touch more pleasant, but also experienced pain relief.

## 5.1 Interactions between human inter-individual touch, oxytocin, and social evaluations of others

Our findings shed light on the complex relationship between oxytocin, touch and social impressions of others. The observation that oxytocin "intensifies" or "sharpens" evaluation of others' mood, both positive and negative, is in line with the view that oxytocin mediates attention to, and interest in, socially relevant stimuli (Shamay-Tsoory, 2010, Kemp and Guastella, 2011). This was reflected by oxytocin-induced increases in stimulus-related pupil dilation responses, which may reflect an increase in attention to these socially relevant stimuli (**Paper II**).

Inter-personal touch has been suggested to intensify sensory information from other modalities (Knapp and Hall, 1997, Hertenstein et al., 2006a). Indeed, we found that concomitant human stroking touch made faces with

neutral or happy emotional expressions appear more attractive and friendly, but angry faces more unattractive and unfriendly (**Paper I**). Interestingly, this "emotional sharpening" effect was evident only after intranasal administration of oxytocin. The touch experience was in turn affected by the emotional expression of the observed faces. Touch was most pleasant when presented together with a smiling face and least pleasant when presented together with a frowning face. Human touch pleasantness was more profoundly influenced than machine touch, again reflecting the significance of human touch in these interactions. Contrary to our hypothesis, we did not find evidence that oxytocin affected touch experience – neither the overall pleasantness nor depending on the facial expression.

Oxytocin is thought to be involved in reward aspects of social processing (Uvnäs-Moberg, 1998, Insel and Young, 2001, Dolen et al., 2013). However, while intranasal oxytocin often influences social behavior and related social cognition, intranasal oxytocin is seldom reported to affect hedonic feelings or mood (but see Shamay-Tsoory et al., 2009). This may point towards other substances being more important for shaping the hedonic experience of touch, e.g. opioids (Løseth et al., In press). However, as the central effects of oxytocin are often reported to be specific to the social domain, oxytocin may play a role in hedonic touch experiences in more naturalistic social settings. A recent study reported that a group of heterosexual men found gentle caresses more pleasant after intranasal oxytocin (Scheele et al., 2014). Interestingly, this effect was limited to caresses they believed were performed by a female experimenter. Oxytocin did not affect the pleasantness of caresses they believed to be performed by a male experimenter, although the same female experimenter, who was blinded to the condition, performed all the caresses. One important difference between that study and ours was that our (male and female) participants were not informed about the identity or gender of the experimenter who performed the touch. However, at debriefing 67.5% of participants (55% of males) believed touch had been administered by a female both times, and only 7.5% believed the toucher was always male.

Similarly to oxytocin treatment, human touch increased pupillary responses to the emotional faces, relative to machine touch. This may reflect the overall salience of human touch we see in these interactions, likely due to the increased pleasantness and/or social relevance of human touch relative to machine touch. The degree to which the pupil effect can be attributed to the physical properties of the human touch stimuli (gentle, CT-optimal, stroking touch) or to the participants' knowledge that another human being was touching them, is not possible to disentangle from the present data.

## 5.2 Oxytocin increases sensitivity to others' subtle and explicit emotional expressions

Consistent with the idea that oxytocin raises the vigilance of socially relevant stimuli, we found that intranasal oxytocin, relative to placebo, sharpened the evaluations of others' mood, such that frowning faces appeared more angry and less happy, while smiling faces appeared happier and less angry. This effect was observed both for faces with explicitly expressed emotions and for faces displaying only subtle emotional cues but otherwise appeared as emotionally neutral. Oxytocin increased stimulus-induced pupil dilation responses to all the presented facial expressions. Pupil dilation has been successfully used as an index of interest, attention allocation or cognitive load (Hess and Polt, 1960, Kahneman and Beatty, 1966, Laeng et al., 2012), and shows close covariation with the firing of neurons in the locus coeruleus (LC), the principal site for norepinephrine synthesis in the brain (Aston-Jones and Cohen, 2005). LC signaling is thought to be particularly important for event detection and is closely related to the 'ventral attention network' (Corbetta et al., 2008). The LC also contains oxytocin receptors (Petersson et al., 1998). Thus, it is possible that the intranasal or endogenous increase of central oxytocin levels causes pupil dilation via direct oxytocinergic actions on neurons in the LC. Although speculative, this may reflect a potentially important mechanism underpinning the crucial role of oxytocin in pair bonding and affiliation (Feldman, 2012). A recent study replicated this finding, and reported increased pupil dilation in response to faces expressing happiness, anger, sadness, and fear, during an emotion recognition task (Prehn et al., 2013). Nevertheless, since both that study and ours included exclusively stimuli containing social information, we cannot know whether oxytocin increases pupil dilation primarily to social stimuli or to salient stimuli in general, regardless of its social relevance.

We found that the oxytocin-induced emotional sharpening effect depended on each individual's ability to distinguish between the implicitly angry and implicitly happy faces at baseline (defined as performance after placebo treatment). Participants with low baseline emotional sensitivity showed robust improvement on task performance, while those with high baseline emotional sensitivity showed little or no improvement from oxytocin. Since performance was measured as a difference in VAS scores, the question of whether there was a ceiling effect in high emotional sensitivity participants is not trivial. Nevertheless, the selective sharpening effect of oxytocin was also supported by a separate analysis using stimulus-induced pupil dilation as an

independent moderator, instead of the emotional sensitivity score. Those with high task-related pupil dilation, likely reflecting increased attentional demands, had the largest oxytocin-induced improvement of emotional sensitivity. Moreover, the finding replicated a recent study using an independent measure of emotional sensitivity. In that study, the effect of oxytocin on a behavioral task assessing empathic accuracy depended on each individual's social-cognitive competence, as measured with the Autism Spectrum Quotient (AQ) (Bartz et al., 2010). Individuals who were less tuned to social information, as indicated by high AQ scores, showed greater oxytocin-induced improvement on the emotional accuracy task. Curiously, autism spectrum score was recently negatively correlated with oxytocin enhancement of touch pleasantness (Scheele et al., 2014).

Findings of oxytocin's effects on emotion recognition and social approach behavior has fueled enthusiasm for intranasal oxytocin as a potential treatment in psychiatric disorders characterized by impaired social functioning, e.g. autism spectrum disorder (Gordon et al., 2013, Preti et al., 2014), schizophrenia (Fischer-Shofty et al., 2013, Davis et al., 2014), depression (Mah et al., 2014, Yan et al., 2014) and drug addiction (Kovacs et al., 1998). While our findings are consistent with the notion that oxytocin may improve social competence, and thereby prove a useful treatment for such clinical populations, little is known about long-term use of intranasal oxytocin, since human experimental studies usually employ one single dose. In light of recent reports of intranasal oxytocin effects on less virtuous social behavior, like in-group favoritism (De Dreu et al., 2011) and jealousy (Shamay-Tsoory et al., 2009), in humans, critics worry that oxytocin may be a "double-edged sword" unsuitable for treatment in these clinical conditions (Miller, 2013, Macdonald and Feifel, 2014).

## 5.3 Subjective utility and its prediction

Being touched by another person means that this person is in close proximity and is likely making an approach. The ability to efficiently decide whether a person is a friend or a foe may therefore be more important if this person touches you. The human touch induced "emotional sharpening" we observed (**Paper I**) may reflect mechanisms important for human affiliation, whereby social or emotional information received while being actively touched by another person may be biased, or sharpened, in order to facilitate a "quick-and-dirty" judgment of them (Tversky and Kahneman, 1974). This is reminiscent of biases in other senses. For example, people tend to over-estimate change in auditory pitch for rising tones, which likely signals an

approaching object, compared to falling tones (Neuhoff, 1998). The reciprocal touch-vision interactions (**Paper I**), which may be oxytocin-mediated (**Paper I and II**), reflect a general principle whereby the brain creates sensations. The brain perpetually draws on all available internal and sensory information in order to build an internal model of the environment. This model is used to guide choices by predicting the outcome of different actions and consequently the affective or hedonic value of these outcomes (Friston and Kiebel, 2009, O'Reilly et al., 2013). In a natural environment, such predictive coding may provide a selective advantage compared to a more exhaustive processing of a full range of "raw" sensory information. Shaping sensation in accord with the predictive model is more energy efficient, and can facilitate rapid decision-making when sensory information is ambiguous or incomplete (Tversky and Kahneman, 1974, Friston and Kiebel, 2009). Thus, sensations are always a product of both sensory activation and top-down regulation, making the brain more of an "interpreter" than a "measuring instrument".

Recently, a predictive coding framework has been employed to account for placebo and nocebo responses to pain (Buchel et al., 2014). Here, placebo analgesia is seen as an instance of an internal predictive model that makes active inferences about the sensory input, based on both the expected and the actual sensory activation. Depending on the magnitude and the precision of the prediction and the incoming afferent signal, the resulting pain is reduced if the treatment is believed to be efficient in suppressing pain. The authors suggested that it might be more meaningful to think in terms of one recurrent system, with modulation at almost every level of sensory processing, than to think in terms of one pain processing (ascending) and one pain modulatory (descending) system. A number of neuroimaging studies have studied placebo responses using experimental paradigms, especially placebo analgesia. Many of these show widespread suppression of somatosensory activity, and also modulation of processing in the spinal cord, which is consistent with such a predictive coding framework.

## 5.4 Placebo improvement of hedonic feelings

We found that expectation-induced increases in the pleasantness of gentle touch may rely on a mechanism similar to that of placebo analgesia (**Paper III**). The suggestion that a nasal spray would "boost" the pleasure of gentle touch induced hyperhedonia, which was associated with enhanced touch processing in sensory circuitry (SI, SII, and pINS). In contrast, fMRI

recordings during pain showed decreased somatosensory processing. Moreover, the magnitude of both hyperhedonic increases and analgesic decreases in somatosensory BOLD responses were associated with the individual strength of the functional coupling between the vmPFC and PAG. This influence of vmPFC-PAG coupling on sensory processing of both pain and pleasant touch may potentially reflect a descending modulatory mechanism perhaps acting at the spinal cord level, facilitating "positive" touch signals and suppressing nociceptive signals (Fields, 2004, Fields, 2007). However, since the PAG has bidirectional connections with a wide range of cortical and subcortical brain regions (Linnman et al., 2011), this modulation may rely on entirely central mechanisms. Further research is needed to pinpoint the exact mechanism whereby placebo-induced engagement of cortical and subcortical circuitry modulates sensory systems, but it is likely to emerge from a synergy of both descending action at the spinal cord level (Eippert et al., 2009b), and the interaction of dopaminergic (Scott et al., 2007, 2008, Schweinhardt et al., 2009) and opioidergic (Levine et al., 1978, Zubieta et al., 2005, Wager et al., 2007, Eippert et al., 2009a) cortico-limbic networks.

The extensive similarities between brain responses during placebo hyperhedonia and analgesia, combined with the positive correlation between behavioral placebo analgesia and hyperhedonia responses, led us to ask whether they arose from a generalized shift in motivational state (Fields, 2004, Fields, 2011). We found that when treatment was suggested to increase the pleasure of positive touch, people reported not only increased enjoyment of touch, but also reduced pain, although there was no mention of analgesic effects, and expectation ratings indicated no explicit expectation of analgesia (**Paper IV**). Conversely, participants who were told that the nasal spray they were about to take would induce pain relief reported both reduced pain and increased touch pleasantness. This is consistent with a view of placebo responses as a generalized mechanism of reward prediction (Fields, 2004, Lidstone et al., 2005, Petrovic et al., 2005). We propose the following mechanism: if a medical treatment is believed to reduce negative symptoms, like pain, this enables the individual to increase their focus on other behaviors, such as reward seeking. As a consequence, the hedonic impact of rewards, like pleasant touch, is also improved. Correspondingly, expecting increased hedonic impact of a reward may reduce the importance, and therefore the unpleasantness, of pain (Dum and Herz, 1984, Benedetti et al., 2013).

## 5.5 Clinical perspectives

In the clinical context, sensory signals (e.g. the clinical environment and treatment devices, the practitioner's white coat, his/her apparent mood, and the meaning of verbal information) interact with the patient's internal processes (e.g. expectation, memories, mood, attention) to influence the action of endogenous modulatory neural systems (Colloca and Benedetti, 2005, Enck et al., 2008). Inter-personal touch and the visual impression of the doctor's face can be conceptualized as nonverbal sensory cues, which can inform the patient's predictions about the outcome of the treatment. The quality of the patient-practitioner relationship can profoundly impact on the outcome of medical treatment across a range of medical conditions (McKay et al., 2006, Kaptchuk et al., 2008, Lynoe et al., 2011).

While most research in the field of medicine has focused on the relief of negative hedonic feelings, like pain or discomfort, the research presented in this thesis suggests broadening the view to also encompass positive hedonics. Inter-individual touch is frequently used to communicate positive messages, like reassurance, comfort, sympathy, and support (Hertenstein et al., 2006b). Consistent with this, socially appropriate touch has been proposed to strengthen placebo effects (Moerman and Jonas, 2002, Jonas, 2011). In human infants (Fairhurst et al., 2014) and mammals (Dunbar, 2010), stroking touch has parasympathetic and anxiolytic effects, which have been proposed to work through oxytocin (Uvnäs-Moberg, 1997, 1998). Interestingly, a recent study reported that oxytocin boosted placebo analgesia, perhaps as a consequence of an increased quality of the interaction with the treatment provider (Kessner et al., 2013). Our findings suggest that oxytocin mediates a bimodal effect of inter-individual touch on the impressions of others (**Paper I**). After intranasal oxytocin, receiving gentle human touch during viewing of faces enhanced both positive ratings of innocuous, friendly faces and negative ratings of frowning, threatening faces.

Since a high quality patient-practitioner interaction relies on a foundation of safety and trust, our findings highlight the importance of the meaning of touch. Inter-personal touch may mediate social bond formation and maintenance through oxytocinergic mechanisms, but this is likely to be dependent on the other available sensory cues (**Paper I**), as well as internal motivational state (**Paper III-IV**). We found broad similarities between the expectancy-induced improvement of positive and negative hedonic feelings, both in subjective reports and in the underlying activation of neural circuitry involved in emotion appraisal and valuation (**Paper III**). Further, we found that the suggestion that a drug would have beneficial effects on positive

hedonics (through a purpose-made video documentary of ~6 min duration) was sufficient to also induce the suppression of negative hedonics (pain), and vice versa (**Paper IV**). Thus, focusing on positive appetitive outcomes of a treatment, such as life quality or regained ability to enjoy pleasures (i.e. alleviation of anhedonia), may suppress negative symptoms as well. Conversely, patients' belief in a treatment's ability to abolish negative symptoms may increase the capacity to enjoy pleasures, which is disrupted in a wide range of psychiatric disorders and chronic pain conditions (Rømer Thomsen et al., in press).

# 6 CONCLUSIONS

**Paper I.** Oxytocin interacted with human gentle touch to sharpen social evaluations of others. The hedonic value of touch from an unseen stranger was in turn shaped by concurrently observed emotional expressions of others.

**Paper II.** Oxytocin increased sensitivity to (subtle and explicit) positive and negative emotional expressions in others, an effect that was stronger in those with low emotional sensitivity at baseline. Oxytocin increased pupillary responses, consistent with the view that this hormone mediates attention to socially relevant sensory cues.

**Paper III.** Placebo improvement of pleasure (hyperhedonia) and pain (analgesia) were underpinned by corresponding up- or down-regulated stimulus responses in sensory circuitry. The functional coupling between prefrontal and brainstem structures correlated with individual magnitudes of both placebo hyperhedonia and analgesia, and the underlying sensory modulation.

**Paper IV.** The expectation that a treatment will increase pleasure induced improvements of both pleasant touch and pain. Conversely, the expectation of analgesia induced both pain relief and increased touch pleasantness.

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