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Investigating the Role of Oxytocin and Opioids in Social Prediction Error Processing: A Placebo-Controlled fMRI Study

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1. Introduction

1.1 The role of the prediction error in learning

To make sense of our surroundings, we must learn which actions lead to which outcomes and which cues are predictive of which consequences (Garrison et al., 2013). This learning must be adaptive, as our environment is incredibly variable and rarely constant (Iordanova et al., 2021). The Prediction Error (PE) is a fundamental component in both reinforcement learning (Lowet et al., 2020) and associative learning (Iordanova et al., 2021). By increasing or decreasing the probability of showing a behaviour or by strengthening or weakening the association between cues and outcomes, PE processing enables us to navigate and engage with our surroundings adaptively. Thus, it is not the reward itself that drives learning, but rather the PE (Garrison et al., 2013; Lowet et al., 2020). The basic PE model was formulated by Rescorla-Wagner in 1973 (Diederen & Schulz, 2015) and can be characterized by the following equation (Lowet et al., 2020):

$$\delta = R - V$$

The PE size (δ) is computed by subtracting the value of the outcome (V) from the prediction (R) (Lowet al., 2020). The equation shows that large PEs reflect a substantial discrepancy between the prediction and the outcome. In contrast, when an outcome was accurately predicted, there is no PE and subsequently, no learning takes place (Garrsion et al., 2013). Furthermore, the equation shows that both positive and negative signs are possible, meaning that PEs can be either positive or negative. A positive PE occurs when an unexpected outcome exceeds the prediction, and accordingly, a negative PE occurs when an unexpected outcome falls short of the prediction (Iordanova et al., 2021).

However, the Model by Rescorla-Wagner is not suited to explain the high-dimensional decision-making scenarios that we face every day and can only account for linear environments (Diederen & Schulz, 2015) because only the mean of the underlying reward distribution is considered (Muller et al., 2024). In reality, however, rewards have fluctuating

probability distributions with varying standard deviations (SD). Thus, it would lead to suboptimal decisions if we modify our behaviour too hastily in response to a few PEs, not knowing the SD. Therefore, prediction errors must also regard the variability (Diederen et al., 2016; Diederen & Schulz, 2015) because otherwise only slow long-term learning rates would be possible (Payzan-LeNestour and Bossaerts, 2011). This deficit of the original model was overcome by the introduction of the distributional reinforcement learning model (distribution RL) by Bellemare, Dabney, and Munos in 2017, by assuming that not only the expected reward is learned but rather the entire probability distribution (Bellemare, Dabney & Munos, 2017). This implies the existence of two different types of neurons encoding different parts of the reward distribution, called the optimistic and pessimistic neurons. Optimistic neurons have expected rewards above the mean and weigh positive PEs higher. Accordingly, pessimistic neurons have expected rewards below the mean and are more sensitive to negative PEs. There is evidence for this non-linearity of PE coding from single-unit recordings in rhesus monkeys showing distinct firing rates and topographic orientation (Muller et al., 2024).

Another distinction that can be made between neurons in the reward learning circuit is between unsigned and signed errors. Unsigned errors only encode the absolute difference between expected and received reward, with the neural activity only reflecting the difference, regardless of whether the prediction exceeds the outcome or vice versa. Signed errors, on the other hand, work directionally, encoding the PE relative to the baseline. When the outcome is greater than the prediction, neural activity spikes and conversely decreases when the outcome falls short of the prediction (Iordanova et al., 2025).

Before turning to the neural substrates of prediction error processing, we first need to consider the concept of value in reinforcement learning, as it plays a central role within the prediction error network. While the prediction error gives immediate feedback, the value indicates long-term desirability by taking all cumulative rewards from the current state onwards into account. This means that we seek to maximize our overall value and not

necessarily the reward frequency. For example, a reward that is rare but immensely pleasurable can have a higher value than a lower reward that is easily obtained. On the network level, the PE is used to update the value in order to inform future decisions, with the PE being the precondition for value estimation (Sutton & Barto, 1998). The value also incorporates the discounting of future rewards depending on their temporal distance from the present. That is, we prefer immediate rewards and we discount rewards the further they lie in the future, which reduces the value in terms of a weighted mean sum of squares (Lowet et al., 2020; Sutton & Barto, 1998). That yields a new formula to describe the PE:

$$\delta(t) := r_t + \gamma V(s_{\{t+1\}}) - V(s_t)$$

The PE adjusted for temporal difference is calculated by replacing the simple reward prediction (R) from the previous formula (δ = R – V) with the term $r_t + \gamma V(s_{\{t+1\}})$. It represents the updated value that is estimated for the next state with r_t being the received reward at the current state and $\gamma V(s_{\{t+1\}})$ being the discounted value of the next state. The discount factor $\gamma \in [0,1]$ determines how strongly future outcomes are considered. To summarize, the expected future reward is already built into the current prediction error $\delta(t)$ (Lowet et al., 2020).

The theory behind PE processing described above, which is used to explain reinforcement learning, is mainly based on computational models (Garrison et al., 2013); however, many correlates can be found in the brain (Hassabi et al., 2017). While the theoretical framework of prediction error processing is grounded in reinforcement learning models, its implementation in the brain reveals a far more dynamic system. Rather than operating in isolation, the prediction error network interacts with broader functional circuits involved in attention, emotion, and executive control. These interactions go beyond what is reflected in computational models.

1.2 Neural Substrates of Prediction Error Processing

In the following chapter, we will explore different brain regions that are important in PE processing in a narrative review-like fashion. To proceed in a somewhat structured manner, we will divide the PE network into functional units proposed by Glimcher et al. (2011): the midbrain, the frontal cortex, and the basal ganglia. The midbrain is the origin of dopaminergic neurons that initially encode the prediction error (PE). From the midbrain, dopaminergic neurons project to the frontal cortex, where expectations and evaluations are processed and value is encoded. In addition, neurons from the midbrain project to the basal ganglia, where the association between stimulus and outcome is processed, and learning is mediated through synaptic plasticity (Glimcher, 2011). However, the following chapter will show that this is a strong simplification that cannot do justice to the complex functions of the PE network. Subsequently, the regions amygdala and insula are discussed, which cannot be assigned based on the classification by Glimcher et al. (2011).

1.2.1 Prediction Error Processing in the Midbrain

1.2.1.1 Ventral Tegmental Area. The ventral tegmental area (VTA) is most likely the primary source of the PE signal (Lerner et al., 2021), which is generated by translating the prediction-outcome difference into a firing rate (Watabe-Uchida et al., 2017). Additionally, the VTA is the primary source of Dopamine in downstream target structures like the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC) (Lammel et al., 2012). By optogenetically tagging dopaminergic neurons in the VTA in mice, Eshel et al. (2015) could show that positive PEs increase the dopaminergic activity in the VTA, negative PEs decrease the activity, and correct predictions do not change it. On that subject, there is also evidence for a unified coding function of PEs, i.e., through subtraction, the same neuron can encode both positive and negative PEs (Eshel et al, 2016). However, this finding is not undisputed, as there is also evidence for neurons in the VTA with distinct functions, namely the optimistic and pessimistic neurons. Single-unit recordings in the VTA revealed variations in

excitability across the dopaminergic neurons, which would allow the representation of all predictions on the reward distribution (Lerner et al., 2021).

1.2.1.2 Substantia nigra pars compacta: It was consensus for decades that the substantia nigra pars compacta (SNc) and the VTA are functionally homogenous (Azcorra et al., 2023). Additionally, SNc and VTA are often analysed as one unit in fMRI analysis. This seems reasonable because SNc and VTA encode the PE using the same subtraction function (Howard & Kahnt, 2018). However, in recent years, it has been shown that the SNc and VTA integrate signals from different brain areas, resulting in different excitatory inputs. While the VTA receives the strongest excitatory inputs from the lateral hypothalamus and the dorsal raphe nucleus, the SNc input predominantly comes from the subthalamic nucleus, the globus pallidus externus, and the zona incerta (Watabe-Uchida et al, 2012). Although the authors do not provide a functional interpretation of these distinct inputs, and to my knowledge, there is no publication discussing the implications regarding PE processing, it seems plausible that there are functional differences. Even if we cannot interpret the differences yet, we can reject the idea that SNc and VTA are homogeneous, with the implication that the areas should be recorded separately in fMRI analysis to further our understanding.

1.2.2 Prediction Error Processing in the Prefrontal Cortex

1.2.2.1 Ventromedial Prefrontal Cortex. The ventromedial prefrontal cortex (vmPFC) is involved in encoding PEs, with studies suggesting that it exclusively responds to positive ones (Combrisson et al., 2023; Rehbein et al., 2023). A transcranial direct-current stimulation study by Rehbein et al. (2023) indicates the involvement of the vmPFC in formulating the prediction of a reward. The authors observed an optimism bias, i.e., the probability of a reward is overestimated during excitatory stimulation of the vmPFC. Excitatory stimulation also led to more behavioural modification in response to positive PEs, emphasizing the role of the vmPFC in positive reinforcement learning (Rehbein et al., 2023). Additionally, the vmPFC is involved in higher-order functions such as goal-directed action selection. By integrating value information

for different rewards or goals from the putamen with the current state, ranks or goal values are assigned and projected to motor areas where they might be translated into actions (O'Doherty, 2011).

1.2.2.2 Dorsolateral Prefrontal Cortex. There is a large functional overlap between the dorsolateral prefrontal cortex (dlPFC) and the vmPFC. The regions show a synergistic interaction with the vmPFC processing positive PEs and the dlPFC predominantly processing negative PEs. While the dlPFC generates a part of the PE activity locally, it receives most of the input from the anterior insula and processes it further (Combrisson et al., 2023). Additionally, the dlPFC might be involved in many higher-order functions concerning decision making or goal-directed behaviour, such as action planning, self-control, and integrating long-term information (Park et al., 2010).

1.2.2.3 Lateral Orbitofrontal Cortex. The lateral orbitofrontal cortex (lOFC) is essential for encoding the identity of predicted rewards, along with additional characteristics of the task state (Howard & Kahnt, 2018). There is evidence for a synergistic link between the lOFC and midbrain regions. Identity expectations from the lOFC are projected into the midbrain, where identity PEs are computed. PE information is then projected back into the lOFC, where further identity predictions are updated (Liu et al., 2024), demonstrating the role of lOFC in learning. The identity PE refers to a mismatch between the expected and the obtained reward, i.e., a different reward is obtained. This does not imply that the value of the unexpected different reward needs to be different (Howard & Kahnt, 2018).

1.2.2.4 Anterior Cingulate Cortex. The anterior cingulate cortex (ACC) is involved in a wide range of functions in PE Processing and RL (Alexander & Brown, 2019; Monosov, 2017). After a cue is presented in a decision-making scenario but before the outcome is known, the ACC encodes the value probability of outcomes in a value-specific manner. There are distinct neurons for positive and negative outcomes, with firing rates proportional to the probability. Additionally, it has been shown that the ACC encodes outcome-uncertainty, with value-

specific neurons having the highest firing rate at maximum uncertainty (Monosov, 2017). Within the ACC, there are also two distinct populations of neurons encoding positive and negative PEs. These PEs are then used to update future reward expectations. They also function as a proxy for outcome-uncertainty, with median PE activity signaling the volatility of a state (Silvetti et al., 2013).

1.2.3 Prediction Error Processing in the Basal Ganglia

1.2.3.1 Dorsolateral Nucleus Accumbens. There are very few studies exploring the role of the dorsolateral nucleus accumbens (dlNacc) in humans. However, Richter et al. (2020) could show that the dlNacc does not respond to the emotional valence of PEs (i.e., better or worse) but to their saliency or unexpectedness. This is in line with the assumption that the dlNAcc generally responds to motivational salience during cue processing. The authors also suggest that the dlNacc in humans is functionally similar to the core Nacc region in rodents and monkeys (Richter et al., 2020). Therefore, the well-established role of the dlNacc in saliency signaling in mice (Kultu et al., 2021) affirms the results by Richter et al. (2020). Further, animal experiments could be used due to their higher experimental accessibility to improve our understanding of the dlNacc in humans.

1.2.3.2 Ventromedial Nucleus Accumbens. A recent review points to a dopaminergic projection from the ventral tegmental area (VTA) to the ventromedial nucleus accumbens (vmNAcc). Contrary to the classical theory that dopaminergic neurons only encode positive prediction errors (PEs), the studies included in the review show that activity in the vmNAcc increases not only in response to positive PEs but also to negative ones. This activation scales proportionally with the unexpectedness of the outcome and is therefore independent of emotional valence. These findings suggest that, similar to the dorsolateral NAcc, the vmNAcc encodes motivational salience (Verharen et al., 2020). However, these findings should be interpreted with caution, as the number of publications is still limited and some report conflicting results. For instance, Richter et al. (2020) also identified the ventromedial

dopaminergic pathway from the VTA to the vmNAcc and demonstrated a functional coupling between these regions. However, they observed a significant increase in activity only in response to positive outcomes.

1.2.4 Basolateral Amygdala

A population of neurons in the basolateral amygdala (BLA) encodes unsigned PEs by increasing their firing rate in reaction to unexpected outcomes, independent of their emotional valence. These PE signals generated in the BLA might be a precondition for the subsequent modulation of attention to cues associated with favourable outcomes (Brockett et al., 2021). The role of the BLA in directing attention was also demonstrated by Esber & Holland (2014). The authors showed that the BLA is crucial in directing attention and increasing motivational saliency in response to negative PEs by bilaterally lesioning the BLA in rats. Rats in the lesion condition were unable to increase cue associability in response to negative PEs, while the response to positive PEs was unaffected by the lesion, highlighting that the BLA is pivotal in saliency processing in negative PE conditions (Esber & Holland, 2014).

Next to general motivational saliency modification for negative PEs, the BLA is also obligatory in the learning of fear. By encoding PEs for unexpected aversive outcomes, the Parvalbumin-expressing GABAergic neurons in the BLA can rapidly form fear associations. When these neurons are optogenetically inhibited in rats, fear learning or the formation of fear associations is significantly dampened (Yau et al., 2021). However, the role of these GABAergic neurons is not limited to learning when to be afraid but also involves learning when not to be afraid (Sengupta et al., 2016; Yau et al., 2021). In contrast to fear learning, a PE arises in situations where a threatening outcome is expected but does not occur. The BLA processes this prediction error to weaken existing fear associations. This function of the BLA has also been demonstrated in animal studies (Sengupta et al., 2016). Sengupta et al. (2016)

showed that when GABAergic neurons in the BLA are chemogenetically manipulated, the relevant prediction errors can no longer be used to suppress fear.

1.2.5 Insula

The prediction of risk and the calculation of risk PEs are located in the insula. Risk PEs and hence the insula are essential for learning, as we adjust our learning rates in response to changes in risk. Analogous to regular PE processing in the dopaminergic system, past risk PEs are being used to update future risk estimations. Risk is defined here as the standard deviation (SD) of a reward around its mean (Preuschoff et al., 2008). For aversive domains, risk PEs are also calculated after the outcome but are predominantly cue-induced, while risk PEs for positive domains are predominantly induced by the outcome. The specific roles in risk processing can be further subdivided within the insula. PEs related to subjectively perceived risk are preferentially encoded in the anterior insula, whereas the mid-insula specifically encodes those linked to objective risk. Furthermore, the anterior insula preferentially encodes cue-induced risk PEs in negative domains, whereas PEs in positive domains are preferentially encoded at the time of the outcome (Kim et al., 2025).

1.3 Social and Non-Social Prediction Error Processing

The majority of studies that have examined the role of the above-described areas in PE processing have used non-social rewards such as food or non-social punishments such as electric shocks. This applies not only to the included studies but also to the broader research landscape on PE processing. A database search in Web of Science yields 337 results for fMRI studies examining non-social reward in prediction error processing and only 41 results for social rewards. Although social rewards are underrepresented in PE processing research, we already know that the PE network is sensitive to social rewards (Poore et al., 2012). This raises the question of whether social PEs are processed in the same way and by the same brain areas as non-social PEs.

A recent meta-analysis by Martinez-Saito & Gorina (2022) compared the brain activity when processing social vs. non-social rewards using ALE (Activation Likelihood Estimation) and SDM-PSI (Seed-based d-Mapping with Permutation of Subject Images). They reported identical activation patterns for social and non-social PEs in the striatum, the medial PFC, and the ACC. The only differences found were the bilateral insula, which only showed significant activation in the social PE domain, and the ventrolateral PFC, where social PEs led to more activation compared to non-social PEs. The authors conclude that social and non-social PEs are a subset of the same learning signal that is identically processed within the same system. They support that claim with a subtraction analysis between social and non-social PE activity with no surviving clusters (Martinez-Saito & Gorina, 2022).

In addition to the meta-analysis outlined above, several individual studies are arriving at the same conclusion. Using an ultimatum game modified to induce social norm PEs, the authors Hétu et al. (2017) could show that the induced social PEs were processed in the same manner as non-social PEs in the VTA and SNc. In a social instrumental task, Solié et al. (2022) came to the same conclusion, showing the importance of dopaminergic neurons in the VTA in social learning and subsequently in socially motivated behaviour.

To my knowledge, there are no studies indicating that social and social PEs are processed by different systems. However, a possible limitation of past studies is the confined spatial resolution of fMRI. It cannot be ruled out that there are distinct subpopulations of neurons encoding social and non-social PEs within the same regions and clusters.

1.4 Modulation by Oxytocin and Naltrexone

Pharmacological manipulation studies have shown the crucial role of oxytocinergic (Kraus et al., 2023) and opioidergic signalling pathways (Korb et al., 2020) in general reward processing. Some studies suggest that these neuromodulators are also involved in PE processing, which seems reasonable considering how closely the processing of rewards and PE coding are intertwined. The sites where Oxy and Nalt affect brain activity are an additional

indicator of their involvement in PE processing. Before looking at the role of these compounds in PE-processing, over the following two paragraphs, an overview of their well-researched effect in reward processing will be provided to approach how they modulate brain activity and to better understand how they also might be involved in the processing of PEs.

Oxytocin enhances the salience of social rewards at the level of wanting (i.e., the anticipation), particularly in response to cues that predict a reward (Bradley et al., 2019; Mickey et al., 2016). Neurobiologically, this effect can be explained by the projection of oxytocinergic neurons to the ventral tegmental area (VTA) and the nucleus accumbens (NAcc), leading to an increased release of dopamine in these regions. This dopamine release has been linked to the facilitation of socially motivated behaviour (Gordon et al., 2011). Beyond its anticipatory effects, oxytocin has also been shown to modulate and enhance the hedonic response to received rewards (Mickey et al., 2016; Scheele et al., 2014). Specifically, oxytocin appears to enhance the perceived salience of received rewards (Kraus et al., 2023). While anticipatory salience primarily pertains to motivational and attentional processes that facilitate reward acquisition (cf. Berridge & Kringelbach, 2015; Yalachkov et al., 2012), the modulation of hedonic salience by oxytocin is better understood as the enhancement of the reward experience itself. Accordingly, oxytocin increases the perceived value of obtained rewards (Kraus et al., 2023). On a neurobiological level, activity in the prefrontal cortex (particularly the ventromedial prefrontal cortex and orbitofrontal cortex) as well as in the anterior cingulate cortex (ACC) and the striatum (particularly the nucleus accumbens) has been associated with the processing of hedonic experiences (Berridge et al., 2015; Kraus et al., 2023; Kruppa et al., 2018; Smith et al., 2010; Ulrich et al., 2023).

The influence of opioids on reward processing can be studied by administering Nalt, a non-specific opioid antagonist (Korb et al., 2020). Research has shown that Nalt can reduce cue-induced reward sensitivity (Weber et al., 2016) and lower the effort exerted to obtain a reward (Korb et al., 2020). Similar effects have been observed for both social and non-social

rewards. Regarding the hedonic response to the consumption of a palatable food reward, Parker et al. (1992) demonstrated a reduction in liking. However, the influence of opioids on wanting and liking is highly complex, leading to diverse effects of Nalt antagonism (Wardle et al., 2016). Concerning social rewards, Nalt can either promote seeking behaviour or induce social indifference, depending on whether an individual feels comfortable or stressed (Loseth et al., 2014). A similar pattern emerges for non-social rewards: while some studies report an increase in food reward liking (Richardson et al., 2005), others show a decrease (Parker et al., 1992). The fact that Nalt antagonizes not only mu-opioid receptors but also kappa opioid receptors (Wardle et al., 2016) could explain the heterogeneity of these results. Additionally, the involvement of many complex systems in reward processing could also be a contributing factor. However, the majority of studies indicate that we can expect a reduction in wanting and liking from Nalt administration.

1.4.1 The Prediction Error Processing and Oxytocin

The limited number of studies examining whether Oxy affects PE processing demonstrate that it does, although the direction of this effect remains inconsistent across findings. Using a reinforcement learning task with a social and a non-social learning condition and different doses of intranasal oxytocin (9, 18, 36 IU), Martins et al. (2022) showed that low doses of Oxy increase PE activity in the sgACC in the prosocial condition, while higher doses of Oxy decrease this activity. A similar dose-dependent effect was found for the functional coupling between the sgACC and the midbrain. Low doses of Oxy increased the functional coupling, and higher doses decreased it (Martins et al., 2022). This could be explained by an inverted U-shaped dose–response of oxytocin that was first suggested by Rilling et al. (2014). Accordingly, low and high doses might decrease the activity in respective areas, while medium doses increase the activity. This might also explain sex dependent differences in response to Oxy, as women and men have different baseline levels (Rilling et al., 2014).

In a probabilistic reinforcement task, Kruppa et al. (2019) tested the modulatory effect of 20 IUs intranasally administered Oxy on the NAcc and the amygdala, comparing adults with autism spectrum disorder with a healthy population. In the autism population, the authors observed an enhanced learning rate under oxytocin, while no significant changes were reported in the healthy control group. On a neural level, Oxy amplified the PE signal in the NAcc but not the amygdala (Kruppa et al., 2019). These findings highlight the role of the NAcc in the processing of saliency in PE coding (Richter et al., 2020) and support the "social salience hypothesis of oxytocin" introduced by Shamay-Tsoory & Abu-Akel (2016). The hypothesis arose from the attempt to integrate various observations regarding the effect of oxytocin on social behaviour into a common explanatory framework, taking contextual factors into account. The authors state that Oxy primarily modifies social behaviour by increasing the salience of social cues. In this process, attention orienting and dopaminergic interaction work together. On the neural level, this can be explained by the interaction between the amygdala, nucleus accumbens, and ventral tegmental area (Shamay-Tsoory & Abu-Akel, 2016). Although the hypothesis was not formulated in the context of PE processing, it nevertheless provides a useful explanatory basis for the effect of oxytocin on PE processing, since salience, as mentioned repeatedly, also plays a significant role in the processing of prediction errors.

To my knowledge, previous fMRI studies that explicitly focused on the PE and Oxy have only investigated the amygdala, NAcc, and ACC. Additionally, results from these studies might not be directly applicable to general PE processing because they were derived from very domain-specific research designs and included higher-order social cognition. However, they serve as an indication of which areas within the PE circuit are modified by Oxy. An additional approach that will be taken in this paper is to look at all areas that are known to be modulated by oxytocin outside of PE processing, which has been investigated by numerous studies, and analyse the overlap with the PE circuit. The meta-analysis by Grace et al. (2018) included 38 fMRI studies that examined changes in brain activity by intranasally administered Oxy. The

included individual studies reported a modulatory effect in the following areas, which overlap with the PE circuit: VTA, ACC, striatum, PFC, amygdala, and insula. While some studies referred to the striatum and PFC as whole structures, others identified specific regions that overlap with the PE-circuit: the NAcc and Putamen within the striatum, and the dlPFC, vmPFC, mPFC, and OFC within the PFC (Grace et al., 2018). Interestingly, for each of the regions mentioned, both increases and decreases in activity were reported depending on the task, sex, oxytocin dose, and type of stimulus. This complexity makes it very difficult to draw general conclusions about how exactly these regions and, consequently, behaviour are influenced by oxytocin. However, the results provide a robust basis for the assumption that oxytocin broadly modulates the PE circuit.

1.4.2 The Prediction Error and Naltrexone

There is a growing body of studies indicating the involvement of the opioid system in the generation of PE signals. Numerous extinction studies with rodents have demonstrated that the blocking of opioid receptors inhibits learning in response to negative stimuli, while learning from positive PEs is increased (Arico & McNally, 2014; Bisby et al., 2020). Similar results were found in humans with opioid antagonism in exposure therapy for specific phobias, inhibiting the improvement of symptoms (Kozak et al., 2007). Although experimental evidence clearly shows that the opioid system plays an important role in encoding PEs, there is still little research on which areas of the PE circuit are influenced by opioids. This is something we will now take a closer look at.

In a relatively early study with rats, microinfusion of opioid antagonists and agonists into the NAcc showed that blocking opioid receptors in a fear learning paradigm led to a reduction in PE activity, while agonism enhanced PE activity (Iordanova et al., 2006). A more recent study by Pecina et al. (2014) with humans examined the modulatory effect of opioids in the context of an experiment on placebo analgesia. According to the authors, the placebo effect can also be understood as a prediction error, i.e. the difference between the expected effectiveness of

the medication and the perceived effectiveness. They could demonstrate that by showing that the placebo effect depended specifically on the PE activity and not only on the expectation. Using μ-Opioid-specific PET Tracers, the authors could also show that the opioid system is actively involved in the processing of PEs. In this regard, they found significant increases in endogenous opiate release during positive PE processing in various ACC regions, OFC, Amygdala, Insula, and the Thalamus. (Pecina et al., 2014). This suggests that the opioid system is broadly involved throughout the PE circuit. Next to the aforementioned areas, opioid receptors are present in many regions within the brain (Pfabigan et al., 2015). It can also be assumed that there is PE-related opioid release in the PFC as well as an opioid–dopamine interaction in the VTA (Wager et al., 2007). Taken together, the findings clearly demonstrate that the opioid system plays a significant or even fundamental role throughout the entire PE circuit, which is why the effects of opioids should be investigated beyond fear and pain paradigms.

1.5 Hypotheses and Research Objectives

Currently, there are only a few individual studies suggesting that Oxy increases PE activity in the ACC and NAcc during social tasks. However, there is substantial reason to assume that Oxy could modulate PE activity across most regions of the PE circuit, as these regions are modulated by Oxy outside of PE processing. Regarding Nalt, we have domain-specific findings indicating that opioids are involved in PE activity across the PE circuit in pain and fear tasks. To my knowledge, however, there are no studies investigating the effects of opioids on social PEs. This would be a plausible assumption, since the regions in which opioids have been shown to play a role in PE processing are also involved in the processing of social PEs.

These research gaps are addressed in the present study by investigating the effect of Oxy and the non-selective opioid antagonist Nalt on PE activity. Based on the theoretical framework outlined in the introduction, we can assume that Oxy increases PE activity in response to social PEs and that Nalt reduces this activity. This is investigated using negative,

rather than positive, social PEs, as this allows us, first, to gain more insight into the mechanism by which PEs are computed, and second, because some areas preferentially process negative PEs, and the opioid system in particular appears to be especially sensitive to negative PEs. Accordingly, the present study tests the following hypotheses:

- **Hypothesis 1:** Neural activity related to negative social PEs is increased under oxytocin administration compared to placebo.
- **Hypothesis 2:** Neural activity related to negative social PEs is decreased under naltrexone administration compared to placebo.

2. Methods

2.1 Participants

The participants were recruited via the participant recruitment system of the University of Vienna. There are several exclusion criteria resulting from the administration of Oxy and Nalt. Despite a low risk to embryos, pregnant women must be excluded. Because a pregnancy is sometimes not recognized immediately, a pregnancy test is conducted at the beginning of each session for female participants before any drug is administered. Participants with a history of drug abuse also must be excluded, as this can alter reward processing at the neural level. Especially, the current use of opiates would distort the results by directly interfering with the signalling of endogenous opioids. To exclude such participants, they were first asked about drug use during screening, and an additional drug test was conducted before the start of each session. Similarly, smokers had to be excluded since nicotine can also alter reward processing.

Additional exclusion criteria result from the experimental design. Participants without normal or corrected-to-normal vision must be excluded because the instructions are presented on a screen inside the MRI scanner. Left-handed people must be excluded because the liking of the social reward is assessed using a button box designed for right-handed individuals. Because social reward was operationalized as a slow stroke on the forearm, and

past research has shown that a touch from the opposite sex is perceived as more rewarding and might also induce sexual reward (Chiappini et al., 2022), we conduct gender matching between the participant and the confederate admin. To ensure effective gender matching, only heterosexual participants can be accepted since homosexual confederates would be otherwise required, which was not feasible within the scope of this study. Because of the stroking on the forearm as social reward, participants with skin conditions in that region must be excluded because it could alter the experience of the social touch. This is also done to protect the experimenter from potentially infectious diseases.

Conventional exclusion criteria for MRI studies are also applied, including metallic implants, work in metal processing, tattoos with iron-based ink, etc. Female participants using an intrauterine device were informed that there is a small risk of the device shifting during the MRI scan and that participation in the study would require the device to be checked by a gynaecologist.

After the exclusion of 3 participants who had to be omitted from the analysis because they did not complete all sessions, the final sample (N=12) consisted of only women with an average age of 25,5 years (SD = 5.7, range = 21–38). After completing all three sessions, the participants received €150 as compensation, which is the conventional amount for 9 hours of time expenditure. If participants withdrew from the study prematurely, they received a prorated compensation of 50 Euros per completed session.

2.2 Materials

2.2.1 Room

There is a separate preparation room to minimize contact between the participant and other members of the experimental team, except for the experimenter. Furthermore, the window between the scanner room and the control room is covered with a curtain to prevent further interaction and distraction of the participant.

2.2.2 Stimulus

As the social reward, a social touch was chosen, as past studies that used reductionistic stimuli such as pictures of smiling faces to induce social reward were less successful in producing significant results (Kraus et al., 2023). The social touch is administered by a confederate disguised as a touch therapist wearing a standard hospital uniform. The social touch is a continuous back-and-forth movement at a speed of 6 cm per second and is administered using the index and middle finger over a 9 cm area on the dorsal side of the right forearm, measuring upwards from the head of the ulna. As less pleasurable stimuli, faster stroking speeds of 21 cm per second and 27 cm per second are used. To assure an accurate stroking speed, the confederate wears headphones that set the pace by indicating the duration of one stroke with a beep. The confederate applies dry powder to the hand to avoid unpleasant rubbing on the participant's skin.

2.2.3 Medication

In the Oxy condition, the participants receive 24 IU of Hexal® (Oxytocin), as this dosage has been suggested to be the most effective (Cardoso et al., 2013). To administer the oxytocin nasally, a PARI SINUS2 nebulizer is used. The inhalation time is 5 minutes per nostril, with the other nostril being sealed with a silicone plug during each inhalation period. According to the manufacturer, the palatal velum should be closed during inhalation. This is accomplished by pronouncing the syllable "-ing" and can be checked by a gentle flaring of the nostrils. In the naltrexone condition, the participants receive a 50 mg pill of naltrexone (Dependex®).

2.2.4 Equipment

Visual instructions were presented on a screen (1280 × 1024 pixels, Flatron L2000CQ, LG Electronics) positioned behind the participant’s head inside the scanner room. A mirror mounted on the 32-channel head coil allowed participants to view the screen during the task. To measure physical effort, as reward probability was directly tied to the exerted force,

participants held a hand dynamometer (HD-BTA, Vernier Software & Technology) in their right hand. In the left hand, participants held a button box (HHSC-2x4-L, Current Designs) used to rate their subjective wanting and liking of the received stimuli. Functional brain images were captured using a 3T MRI scanner (MAGNETOM Skyra, Siemens Healthineers).

2.3 Procedure

Overall, the participants complete three separate sessions, receiving Oxy, Nalt, and placebo in randomized order. In each session, participants take a pill and inhale, ensuring they cannot identify the conditions. In a double-blind fashion, the experimenter also does not know which medication is the active compound and which is the placebo, to avoid experimenter effects.

2.3.1 Preparation

Upon arrival, the participant is escorted to the bathroom where a urine sample is provided, which is brought to another member of the experimental team who completes the pregnancy and drug test. Afterward, they are taken to the preparation room to complete the informed consent and safety form. Although a pre-screening has been conducted, the participant is again asked about medical conditions and procedures relevant to the experiment. The focus here is primarily on scenarios such as a new intrauterine device, a new tattoo, or pricing. In addition, we refrain from testing individuals who are suffering from a severe cough, as this is likely to compromise image quality.

Once the results of the pregnancy and drug tests can be read and it has been confirmed that the participant is eligible for testing, the substances are administered. The subsequent course of the experiment must be precisely aligned with the latency and duration of action of the compounds. Orally administered Nalt has a latency of approximately 60 minutes (Sudakin, 2016) and a half-life of about 4 hours (Meyer et al., 1984), while intranasally administered Oxy has a latency of around 30 minutes and a clinically relevant window of effectiveness of approximately 90 minutes (Smith et al., 2019). Accordingly, Nalt (or the

placebo) is administered first, followed 30 minutes later by Oxy (or the placebo). The experimental task should begin exactly 30 minutes after the inhalation of Oxy is completed, as both substances reach their peak effect at this point. Due to the relatively short duration of Oxy´s effectiveness, delays should be avoided. Inhaling Oxy is not entirely straightforward, as it is often perceived as unpleasant. The experimenter must ensure that participants breathe in exclusively through the nose during the inhalation period and refrain from blowing their nose during or immediately after inhalation, as this could reduce the effect of the oxytocin.

2.3.2 fMRI task

Approximately 10 minutes before the start of the task, the participant is accompanied to the scanner room, where a qualified scanner user conducts a comprehensive fMRI safety check. Once the participant has been cleared for scanning by the qualified user, a confederate introduces herself as a touch therapist and prepares their arm for the administration of the touch reward by measuring and marking a point 9 cm proximal to the ulnar head on the dorsal side of the forearm. Following this, the exact task structure is explained to the participant.

The task consists of one practice block with two trials and two experimental blocks with 16 trials each. All trials last about 38 seconds and follow the same structure (Figure 1). Every trial begins with a brief fixation cross period, after which a reward that can potentially be obtained is announced on the screen. The participant must first rate how much they want the reward using a button box and then exert effort using a hand dynamometer. The percentage of their maximum voluntary contraction (MVC) exerted corresponds to the probability of receiving the announced reward. The outcome is then displayed, and the reward is delivered after a short preparation period. According to the experimental design, either the announced reward or a less pleasant one can be received. Moreover, only reward levels one or two are announced. If reward one is announced, reward levels 1, 2, or 3 can be obtained, and if reward two is announced, either reward 2 or 3 can be obtained. After receiving a reward, the

participant rates it on a continuous scale using the button box. A brief relaxation period follows before the next trial begins.

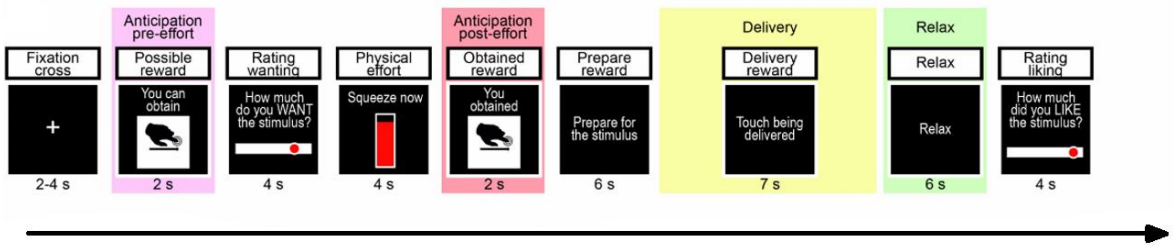

Figure 1. *Trial sequence for the social reward (Chiappini et al., 2022)*

The participant's MVC is assessed before the task starts, once they are already in the scanner. They are instructed to squeeze as forcefully as possible, but still in a reproducible way, three times. The average of these three measurements is used as the participant's MVC. The MVC is reassessed at the end of the task to account for potential fatigue throughout the experiment, allowing for mathematical correction of the performance decline. During each effort phase across the trials, a bar is displayed for 3 seconds, showing the participant the percentage of their MVC that they are exerting. It is essential that force is maintained over the entire three-second period, as only the peak value is recorded. Shorter durations could inflate the peak effort readings as a greater force can be exerted.

To enable the delivery of the touch reward while the participant is lying in the scanner, their arms must remain extended alongside their body with their hands resting on their lower abdomen, as this position provides the confederate access to the marked area on the forearm. It is also important that neither arms nor legs are crossed, as this could lead to magnetic field interactions and cause image artifacts.

2.4 Ethics

The procedure of this study is approved by the ethical committee of the Medical University of Vienna. Every participant is informed about potential risks related to the administration of Oxy and Nalt. In this regard, a study physician is available who is familiar with the details of the experiment and will attend to the participant in the unlikely event of any

side effects. Additionally, the participants are informed about how the collected data is stored and used. They also know that they can withdraw from the study at any given time without consequences. As outlined in the participant section, participants receive compensation on a pro rata basis to ensure they do not feel incentivized to continue participating in case of discomfort to receive a payment.

2.5 Data Analysis

The whole brain analysis, including first and second level estimations, was performed in SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) implemented in MATLAB R2023a (MathWorks Inc.). Additional ROI analysis was conducted in MARSBAR_45 (MARSeille Boîte À Région d'Intérêt) implemented in the SPM12 toolbox

2.5.1 First-Level Analysis

Before the data analysis, the data were recoded to reflect the individual preferences of the participants. If a participant preferred reward two or reward three the most, that reward was assigned to rank 1, and the ranks of the other rewards were shifted accordingly. The cleaned fMRI data from trials where a PE occurred, i.e., when the reward one (6 cm/s) was announced and reward two (21 cm/s) or three (27 cm/s) was administered, or when reward two was announced and reward three was administered, were selected in the model specification. This procedure was repeated for every participant and every condition. With the specification completed, the models were estimated, and contrasts were calculated for "Prediction Error vs. Fix Cross" and "No Prediction Error vs. Fix Cross". The PE activity was contrasted against the activity during the fixation cross, as it can be assumed that the PE circuit shows baseline activity during that time.

2.5.2 Second-Level Analysis

A 3 x 2 full-factorial model was specified with treatment (Oxy, Nalt, placebo) and prediction error (No PE, PE) as factors. For the model estimation, the first-level contrast images (voxel size: $2 \times 2 \times 2$ mm^3) corresponding to each cell of the factorial design were

submitted to the analysis. To test whether oxytocin increases PE-related activity compared to placebo (Oxy > Pla), and whether naltrexone decreases PE-related activity compared to placebo (Nalt < Pla), the following t-contrasts were specified:

- *Oxy* > *Pla*: [0 1 0 0 0 –1]
- *Nalt* < *Pla*: [0 0 0 –1 0 1]

Second-level inference was performed at the whole-brain level with a cluster-defining threshold of $p < 0.05$ (uncorrected). Family-wise error correction (FWE) at the cluster level ($p < 0.05$) was applied to control for multiple comparisons.

2.5.3 ROI-Analysis

ROI-Analysis was used to test the hypotheses that activity in the PE-circuit is (1) increased under oxytocin compared to placebo and (2) decreased under naltrexone compared to placebo. ROIs were defined as spheres with a radius of 6 mm, centred around MNI coordinates reported in previous studies on PE processing (see Table 1). Neurosynth was used to verify that the coordinates lie within the regions of interest.

Table 1. *MNI coordinates for the ROIs included in the analysis.*

ROI	x	y	z	Source
VTA_l	-9	-18	-18	Groppe et al. (2013); Krebs et al. (2009)
VTA_r	9	-18	-18	
SNc_l	-11	-10	-21	Richter et al. (2020)
SNc_r	11	-10	-21	
vmPFC_l	-6	51	-6	Kohl et al. (2019)
vmPFC_r	6	51	-6	
dlPFC_l	-45	27	27	Kohl et al. (2019)
dlPFC_r	45	27	27	
lOFC_l	-22	33	-22	Henssen et al. (2016)
lOFC_r	22	33	-22	
ACC_l	-10	50	-4	Garrison et al. (2013)
ACC_r	10	50	-4	

dlNAcc_l	-13	11	-7	Richter et al. (2020)
dlNAcc_r	13	11	-7	
vmNacc_l	-8	12	-10	Richter et al. (2020)
vmNacc_r	8	12	-10	
BLA_l	-29	-2	-26	Jang & Kragel (2025)
BLA_r	29	-2	-26	
Insula_l	-30	22	-10	Garrison et al. (2013)
Insula_r	30	22	-10	

The ROI analysis was performed using MarsBaR, based on the second-level design matrix estimated in SPM. Contrast values were extracted from the aggregated contrast images computed at the group level. The same contrast vectors as in the whole-brain analysis were applied as t-contrasts to directionally test the hypotheses.

3. Results

3.1 Whole-Brain Analysis

3.1.1 Whole-Brain Analysis (Oxy > Placebo)

At the set level, the contrast *Oxy* > *Placebo* did not yield a statistically significant activation pattern (p = .942), indicating that the observed global brain activity at the time of PE under Oxy-modulation does not differ from activity at the time of PE in the placebo control after correcting for the search volume. At an uncorrected voxel-wise threshold (p < .005), 56 local peak-level loci were identified. However, none of these clusters survived FWE correction, indicating that there is no robust evidence for Oxy's enhancement of PE activity at the whole-brain level when controlling for multiple comparisons.

3.1.2 Whole-Brain Analysis (Nalt < Placebo)

The contrast *Nalt* < *Placebo* yielded a significant effect (p = 0.019) at the set level, indicating that on a global level, naltrexone did reduce the brain activity at the moment of prediction error coding. Based on this metric alone, we cannot yet determine whether the

reduced activity is localized within the PE circuit. At an uncorrected voxel-wise threshold ($p < .005$), 84 local peak-level loci were identified. Similar to the oxytocin condition, none of these clusters remained significant after FWE correction.

3.2 ROI Analysis

3.2.1 ROI Analysis (Oxy > Pla)

The analysis (Table 2) revealed a significant increase in PE-activity in the right dlNAcc ($t = 1.73$, $p_{uncorrected} = .045$) under Oxy modulation; however, this effect did not survive FWE correction. Additionally, the uncorrected results show a statistical trend towards increased PE-activity in the left dlNAcc ($t = 1.63$, $p_{uncorrected} = .054$), the left and right vmNAcc (vmNAcc_l: $t = 1.38$, $p_{uncorrected} = .087$; vmNAcc_r: $t = 1.55$, $p_{uncorrected} = .063$), and the right basolateral Amygdala ($t = 1.6$, $p_{uncorrected} = .058$). Anatomical masks for the right dlNAcc and the four trend-level ROIs are visualized in Figures 2-6. Additionally, the contrast value and the t-statistic have a positive sign in all regions except for the dlPFC_l, dlPFC_r, and lOFC_l. This shows that in our sample, Oxy modulation increased PE-activity in most areas within the PE circuit.

Table 2. *Overview of all ROI contrasts for (Oxy > Pla)*

ROI	CV	*t*	$p_{\_uncorrected}$	$p_{\_corrected}$
ACC_l	0.9	0.69	0.245932	0.996466
ACC_r	0.52	0.39	0.347715	0.999806
Insula_l	0.59	0.6	0.274941	0.998388
Insula_r	0.03	0.03	0.486464	0.999998
Snc_l	0.76	1.26	0.106875	0.895709
Snc_r	0.64	0.95	0.171787	0.976941
VTA_l	0.48	0.97	0.168403	0.974981
VTA_r	0.19	0.51	0.304727	0.999303
blAmygdala_l	0.9	1.14	0.129057	0.936934
blAmygdala_r	1.35	1.6	**0.056753***	0.689183
dlNacc_l	1.16	1.63	**0.054404***	0.673325
dlNacc_r	1.11	1.73	**0.04466****	0.598986
dlPFC_l	-0.6	-0.37	0.644946	1.0
dlPFC_r	-0.11	-0.09	0.534286	1.0
lOFC_l	-0.14	-0.11	0.542209	1.0

lOFC_r	1.2	0.86	0.196727	0.98749
vmNacc_l	1.01	1.38	**0.086631***	0.836723
vmNacc_r	0.96	1.55	**0.063411***	0.730236
vmPFC_l	1.74	0.81	0.209145	0.990839
vmPFC_r	1.2	0.67	0.251906	0.996986

Note. CV = contrast value. ** $p < .10$ (statistical trend). * $p < .05$ (statistical significance).

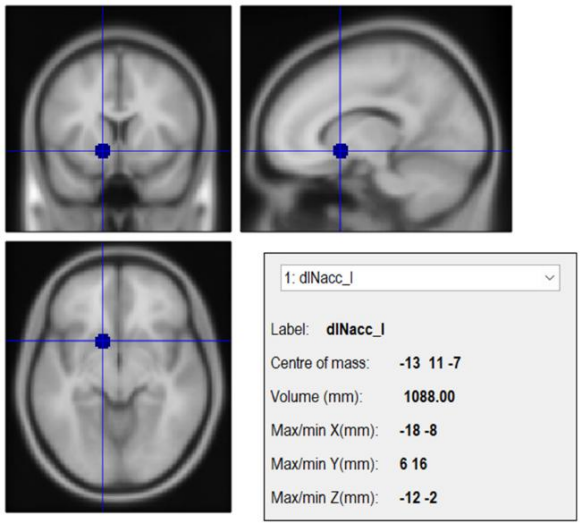

Figure 2. *MNI mask for the left dlNAcc.*

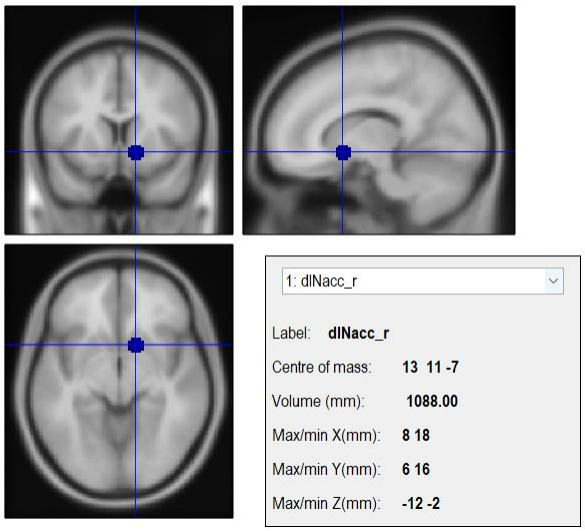

Figure 3. *MNI mask for the right dlNAcc.*

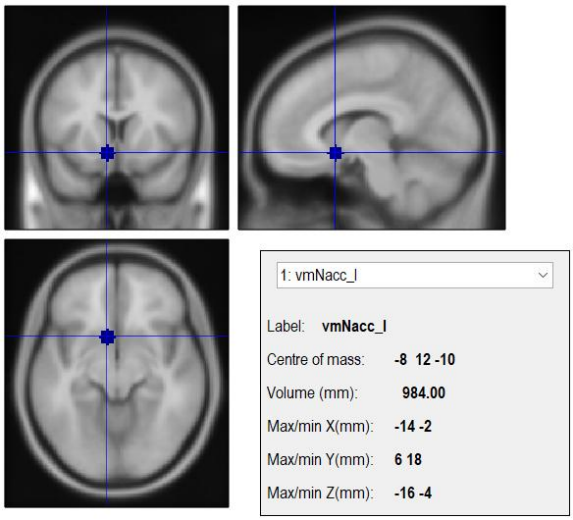

Figure 4. *MNI mask for the left vmNAcc*.

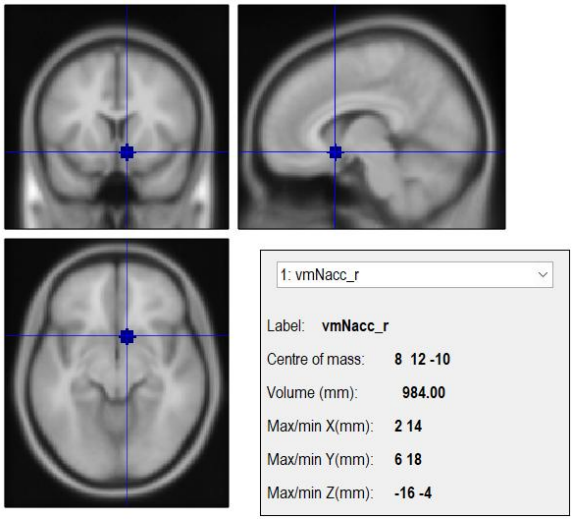

Figure 5. *MNI mask for the right vmNAcc*.

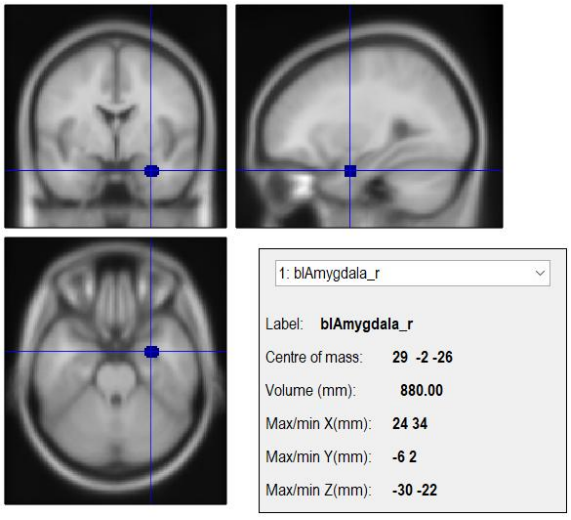

Figure 6. *MNI mask for the right BLA*.

3.2.2 ROI Analysis (Nalt < Pla)

The analysis (Table 2) did not yield any significant results. However, there is a statistical trend for reduced activity in the right SNc (t = 1.29, p = .100). The anatomical ROI mask is displayed in Figure 7. The large, directionally incongruent t-value of the left dlNAcc (t = 1.69; p = .950) indicates an effect opposite to the hypothesis. If we reverse the contrast to Nalt > Oxy (0 0 0 1 0 –1), we observe that PE activity is significantly increased under Nalt modulation in the left dlNAcc (t = 1.69, p = .050). However, this effect does not survive FWE correction. Overall, ROI activity under naltrexone modulation does not align well with the hypothesis that PE activity is reduced, as 16 out of 20 ROIs in the sample show an increase in PE activity.

Table 3. *Overview of all ROI contrasts for (Nalt < Pla)*

ROI	CV	*t*	$p_{\_uncorrected}$	$p_{\_corrected}$
ACC_l	-0.58	-0.62	0.731064	1.0
ACC_r	-0.08	-0.09	0.535584	1.0
Insula_l	0.53	0.76	0.225172	0.993917
Insula_r	0.44	0.74	0.2314	0.994824
Snc_l	-0.25	-0.58	0.717194	1.0
Snc_r	0.62	1.29	**0.100206 ****	0.878978
VTA_l	-0.13	-0.35	0.636419	1.0
VTA_r	-0.01	-0.04	0.514695	0.999999
blAmygdala_l	-0.69	-1.22	0.886498	1.0
blAmygdala_r	-0.33	-0.54	0.704276	1.0
dlNacc_l	-0.86	-1.67	0.950146	1.0
dlNacc_r	-0.55	-1.19	0.880619	1.0
dlPFC_l	-0.33	-0.29	0.613031	1.0
dlPFC_r	0.49	0.52	0.301373	0.999233
lOFC_l	-0.62	-0.68	0.752059	1.0
lOFC_r	-0.87	-0.87	0.806261	1.0
vmNacc_l	-0.59	-1.11	0.864303	1.0
vmNacc_r	-0.47	-1.07	0.854633	1.0
vmPFC_l	-1.03	-0.67	0.747859	1.0
vmPFC_r	-0.32	-0.25	0.597979	1.0

Note. CV = contrast value. ** p < .10 (statistical trend). * p < .05 (statistical significance).

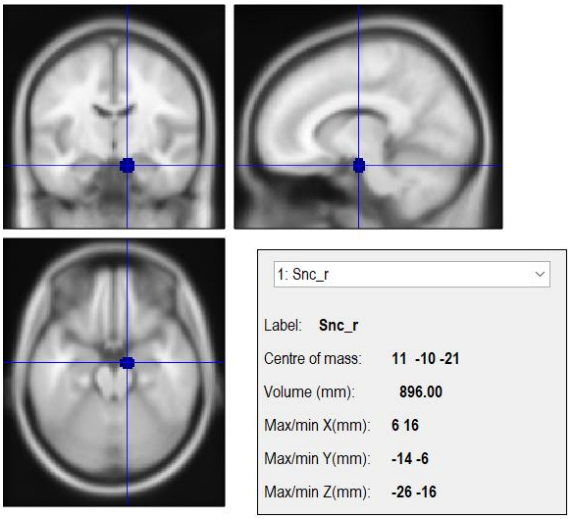

Figure 7. *MNI mask for the right SNc*.

4. Discussion

4.1 Summary of Main Findings

The present study aimed to investigate how the administration of Oxy and Nalt modulates the processing of negative social PEs, using a social touch paradigm in a double-blind, placebo-controlled within-subject fMRI design. Participants exerted effort to obtain desirable rewards and were, throughout the task, exposed to unexpectedly low-value social stimuli. Two main hypotheses were tested: (1) that oxytocin increases PE-related brain activity, and (2) that naltrexone reduces it.

4.1.2 Hypothesis 1

The results partially support the hypothesis that oxytocin increases PE-activity. The ROI analyses showed a significant increase in PE-related activity under Oxy modulation in the right dlNAcc, with trend-level increases in the left dlNAcc, vmNAcc, and right BLA. However, those findings did not survive FWE correction. Also in support of the hypothesis, a numeric increase of PE-related activity was observed. It must be acknowledged that the findings can only be generalized to a limited extent. With only 12 participants, the study was severely underpowered, especially for detecting small pharmacological effects in fMRI. This lack of

power makes it inherently difficult to observe robust effects that survive correction for multiple comparisons.

The whole-brain level yielded 84 significant local peak-level clusters, which also did not survive FWE correction. Also, no significant global effect was found. This lack of whole-brain significance can likely be attributed to the limited sample size in combination with the nature of whole-brain analysis, which tests each voxel independently, with each voxel just representing 8 mm^3 of brain tissue. As a result, the small but consistent effects that were demonstrated in the ROI analysis can be overshadowed by noise and fail to reach significance in the voxel-wise comparison.

4.1.3 Hypothesis 2

The results, for the most part, do not support the hypothesis that naltrexone decreases PE-activity. While the whole-brain analysis suggests a significant global reduction in brain activity at the moment of PE-coding, no specific conclusions can be drawn from that result regarding the PE-circuit. The only result in favour of the hypothesis yielded by the ROI analysis is a statistical trend for the reduction of PE-related activity in the right SNc. The numerical contrast values in our sample suggest an increase in PE activity in most areas within the PE circuit. Furthermore, post hoc analysis revealed a significant increase in PE-activity at the uncorrected level in the dlNAcc. Taken together, the results do not support the hypothesis (2) and contrast with previous studies.

4.2 Interpreting the Results

4.2.1 Interpreting the Results of Oxytocin

4.2.1.1 Significant and trend level findings. The results show that Oxy modulation exclusively increases activity in salience-processing regions of the PE circuit. The well-established notion that oxytocin enhances the salience of social stimuli provides a strong theoretical basis for interpreting these results. The significant increase in PE-related activity in the right dlNAcc clearly supports the findings of Richter et al. (2020) that the dlNacc does not

respond to the emotional valence of PEs but rather to their saliency or unexpectedness. The current study provides critical support for this assumption, as Richter et al. (2020) are, to my knowledge, the only authors who have investigated the role of the dlNAcc in PE processing in humans, and their finding had previously stood as an isolated result

The statistical trend in the vmNAcc sheds light on a mixed pattern of past findings. While Verharen et al. (2020) could show that vmNAcc, similar to the dlNAcc, processes PEs based on motivational salience, Richter et al. (2020) reported involvement only in the processing of positive PEs. Since the present task exclusively included negative PEs, we can assume that the vmNAcc also responds to negative PEs and subsequently encodes motivational salience

The observed trend-level increase in PE-related activity in the right BLA under Oxy modulation supports the assumption that the BLA encodes unsigned PEs independent of emotional valence and is crucial for directing attention and increasing motivational salience in response to negative PEs (Esber & Holland, 2014). The present findings also contradict Kruppa et al. (2019), who did not find an effect of Oxy on the Amygdala and concluded that the modulatory effect is confined to strongly aversive stimuli. As the BLA might be a precondition for directing attention to cues associated with favourable outcomes (Brockett et al., 2021), the present results indicate that Oxy modulates attention and saliency very high upstream, possibly exerting an effect on activity in various downstream areas. Besides PE coding and modulation of attention, the BLA has also been implicated in subsequent learning processes. Although learning was not assessed in the task, based on existing literature (Rosenberger et al., 2019) we can assume Oxy modulation increases the learning rate in reinforcement learning and associative learning, both of which fundamentally rely on PE processing.

Taken together, the results of the Oxy modification show an increase in activity in areas that calculate PEs not based on the difference in emotional valence between prediction and outcome, but based on unexpectedness and salience. This clearly refutes accounts that the PE activity of dopaminergic neurons simply increases in response to unexpected positive outcomes and decreases in response to unexpected negative outcomes, as was suggested by classic theories (Verharen, 2020). The results demonstrate the widely distributed encoding of unsigned PEs that are independent of the emotional valence. Outside of PE processing, the results are in line with the "social salience hypothesis of oxytocin" introduced by Shamay-Tsoory & Abu-Akel (2016). The hypothesis states that the effect of Oxy on our behaviour can be explained by Oxy increasing the salience of social cues. Factors such as attention orienting and dopaminergic interaction play a role in this process, which can be explained at the neural level by an interplay between the amygdala, NAcc, and VTA (Shamay-Tsoory & Abu-Akel, 2016). However, Shamay-Tsoory & Abu-Akel (2016) did not include the PE in their theory. The present study demonstrates that Oxy increases activity in areas that process salience in response to social PEs. Furthermore, the results suggest that the Oxy-mediated increase in saliency of social stimuli might act through the PE-system itself rather than by just modifying attention orienting. While Shamay-Tsoory & Abu-Akel (2016) postulate that Oxy modulates early stages of attentional processing, while also acknowledging motivation, the present results suggest that it might be amplified PE activity that increases the salience of social cues. The "social salience hypothesis of oxytocin" also describes the increase in saliency under Oxy modulation as a more bottom-up process, while the present results suggest a complementary or alternative top-down pathway, in which PEs from past states inform salience and cue associability in future states. In this regard, it can be ruled out that the present study actually measured cue or saliency processing instead of the PE, because the BOLD signal at the time of the outcome was isolated. Further, only trials in which PEs

occurred were included in the analysis, and the time interval between the cue (i.e., the announcement which reward can be obtained) and the outcome was ten seconds.

4.2.1.2 Non-Significant Results. The results show no significant or trend-level effect of Oxy on PE activity in the prefrontal cortex. This is surprising because there are multiple accounts that Oxy increases the learning rate in social tasks (Parr, 2014; Chini et al., 2014), and learning from PEs takes place predominantly in the prefrontal cortex (Glimcher et al., 2011). There are multiple explanations for that. On one hand, as mentioned before, the effect of Oxy is not linear but instead follows a U-shape (Rilling et al., 2014). It cannot be ruled out that the dosage of 24 IUs is not the most conducive for learning. Another explanation is that learning rates are not increased for all types of rewards or even all types of social rewards under Oxy modulation. Liao et al. (2021) found that 24 IU of oxy (the same dosage as in the present study) increased prosocial learning that benefits others but decreased learning that only affects oneself. Additionally, the type of stimulus used in the task might explain the absence of an effect in the prefrontal cortex. While past studies examining the impact of Oxy on learning used high-value rewards (Martins et al., 2022) or aversive stimuli (Zhou et al., 2024) in the present task, unexpectedly low-value social touch was used to induce PEs. This could mean that the PE signal was not strong enough to produce a significant result in the prefrontal cortex or that prefrontal areas process PEs highly valence and value specific which was demonstrated by multiple studies (Combrisson et al., 2023; Monosov, 2017; Rehbein et al., 2023) and the emotional valence in the present task was not strong enough to create a PE signal in the prefrontal cortex.

4.2.2 Interpreting the Results of Naltrexone Modulation

The only ROI that showed a trend towards reduced PE-activity was the right SNc. The fact that there was no suppression in the VTA supports the notion that the SNc and the VTA are not functionally homogenous (Watabe-Uchida et al, 2012). However, based on the data, it cannot be determined whether the reduced activity in the right SNc is due to antagonism of

opioid receptors within the SNc itself or due to antagonism in areas such as the subthalamic nucleus, the globus pallidus externus, and the zona incerta, which, according to Watabe-Uchida et al. (2012), project to the SNc.

The fact that, besides the right SNc, no results support the hypothesis, in combination with a lack of literature, makes it difficult to interpret the non-significant results in a meaningful way. The absence of significant PE-suppressing effects and the increase of PE-activity in most areas within the PE-circuit in our sample is surprising, considering that past studies, as mentioned above, have shown that the opioid system is broadly involved in PE processing (Pecina et al., 2014) and that opioid antagonism reduces PE activity (Iordanova et al., 2006). The results might be explained by a domain-specific role of endogenous opioids, as past studies mainly used fear (Iordanova et al., 2006) and pain (Pecina et al., 2014) stimuli, whereas the present study employed a social touch paradigm involving mildly aversive expectancy violations. One possible interpretation is that the modulation of PEs by opioids only occurs in response to outcomes with very strong positive or negative emotional valence. This would imply a functional heterogeneity within the PE network, where certain domains or PEs of different emotional valence may be more or less dependent on opioid modulation. On the other hand, there might be the possibility that opioids do not play a decisive role in the processing of social prediction errors. It is also possible that potential effects are simply too small for the statistical power of the present study.

Surprisingly, the post-hoc analysis revealed a significant increase in PE activity at the uncorrected level in the left dlNAcc under opioid antagonism. This finding contradicts previous studies that associate opioid antagonism exclusively with reduced PE activity (Iordanova et al., 2006), as well as studies linking strong PE signals to increased opioid release (Pecina et al., 2014). This highlights the complex and multifaceted role of opioids (Wardle et al., 2016). Currently, there are no findings from the PE processing literature that could explain this result. However, in the context of reward processing, it has been shown that

Nalt can enhance social seeking behaviour when the individual is under stress (Loseth et al., 2014), which is to be expected when lying in an fMRI scanner. This seeking behaviour might translate into increased PE activity in the dlNAcc, which in turn would suggest heightened saliency processing.

Another surprising finding is that not a single region within the PE circuit showed significantly reduced PE activity, while global brain activity at the time of PE processing exhibited a significant suppression. This could indicate, on the one hand, that the PE system for social expectation violations is not primarily opioid-dependent, and on the other hand, reflects the widespread distribution of opioid receptors across the brain. It is possible that effects within the PE system result from secondary modulation via projections into the PE circuit.

4.3 Implications for future research

4.3.1 Prediction Error Modulation by Oxytocin

The present study provided insights into how Oxy modulates PE processing in response to negative social PE, with effects exclusively in regions associated with attention and (motivational) saliency processing. However, the results have to be interpreted with caution, as none of the observed effects survived FWE corrections, which can be attributed to the small sample size (N = 12), limiting statistical power and generalizability. Future studies should replicate these findings with larger and more diverse samples to obtain robust results.

Regarding the effect of Oxy on PE processing, it remains unclear whether Oxy also modulates non-social PEs. While the present study focused exclusively on social stimuli, there is reliable evidence that Oxy also modulates non-social reward processing (Harari-Dahan & Bernstein, 2014). However, if and how Oxy modulates the processing of non-social PEs has not been examined yet. Future research should examine non-social PE processing under Oxy modulation to test for domain-specific effects. A within-subject design with both social and non-social conditions would produce informative results.

The current study offers new insights into the *Social Salience Hypothesis of Oxytocin*. The increased activity in regions processing unsigned PEs and modulating attention and saliency suggests that the enhanced salience of social stimuli following the administration of Oxy could be mediated by the PE system itself. Future studies should therefore explore whether PE processing represents the central mechanism through which Oxy enhances the salience of social cues.

Finally, the findings highlight the potential of Oxy as a treatment for autism spectrum disorder, regarding the reduced social salience, which is a core feature of the condition (Corbett et al., 2023). The finding that Oxy increases the activity in salience-encoding regions such as the nucleus accumbens and the amygdala suggests that increasing saliency PEs via Oxy administration might represent a promising target mechanism. However, more research is needed to examine whether these neural modulations translate into meaningful improvements in social learning and engagement in autistic populations.

4.3.2 Prediction Error Modulation by Naltrexone

While prior work suggests that negative PEs are associated with increased opioid release and demonstrates that opioid antagonism reduces PE activity (Iordanova et al., 2006), the present study has shown that the relationship between opioid signalling and PE processing might be highly domain-specific and context-dependent. In this regard, the results, especially the significant increase in PE-activity in the left dlNAcc, might indicate that the modulatory role of opioids is different for the processing of social and non-social PEs. Additionally, the reduction in global activity, without a significant decrease within the PE circuit, might indicate that opioids exert a general upregulation of brain activity with little direct task-related modulations for social PEs.

Overall, the findings raise more questions than they answer and highlight how little is currently known about the role of endogenous opioids in PE processing, particularly in the

social domain. Substantial empirical work is needed before meaningful theoretical models can be developed.

4.4 Limitations

The randomized within-subject, placebo-controlled design is a major strength of the present study because it allows for robust control of interindividual variability. Additionally, while being highly standardized, the social touch paradigm consists of non-reductionistic stimuli that approximate real-world social reward closer than other stimuli that have been used as social rewards.

However, several limitations must be acknowledged. Especially, the small sample size (N=12) limits the generalizability of the results and increases the risk of type-I or type-II errors. Another limitation is that the sample only consisted of women, which reduces the applicability of the results to men, as it has been shown that men and women respond differently to Oxy (Grace et al., 2018). Another limitation arises from using the same reward over many trials, as the value of that reward might drop over time, which in turn could reduce the intensity of the PE activity. Similarly, the value of the social touch might be relatively low for some participants from the beginning, since the rewards, although close to real-world affectionate scenarios, are still artificial, which would also reduce the intensity of the PE activity.

Additionally, the task used in the present study did not capture the learning rate, which would allow conclusions about whether the observed neurological effects are also functionally relevant in the modification of behaviour and learning. This would be relevant as it has been shown that neuromodulators can affect neural processes without necessarily altering conscious perception or behaviour (Kraus et al., 2023). Therefore, including behavioural measures in the design would allow for better judgment of the impact of the present results.

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Abstract German

Vorhersagefehler (PEs) kodieren die Differenz zwischen erwartetem und tatsächlichem Ausgang (Outcome) und sind somit eine grundlegende Komponente adaptiven Lernens. Die Mechanismen des PE wurden in der computationalen Neurowissenschaft umfassend modelliert, und es gibt umfangreiche, wenn auch nicht erschöpfende Evidenz zu den an der PE-Verarbeitung beteiligten Regionen und ihren spezifischen Rollen innerhalb des PE-Schaltkreises. Die breite modulatorische Funktion von Oxytocin (Oxy) und Opioiden in der Belohnungsverarbeitung sowie einige erste Studien deuten darauf hin, dass diese beiden Neuromodulatoren auch eine entscheidende Rolle in der PE-Verarbeitung spielen. Es gibt eine solide theoretische Grundlage sowie einige erste empirische Befunde, die nahelegen, dass Oxy die PE-Aktivität als Reaktion auf soziale Erwartungsverletzungen verstärkt. Die Rolle von Opioiden in der PE-Verarbeitung wurde bisher nur für nicht-soziale Ausgänge untersucht. Da Opioide jedoch die Verarbeitung sozialer Ausgänge modulieren, ist es naheliegend anzunehmen, dass auch soziale PEs moduliert werden. Folglich testet die vorliegende Studie die Hypothese, dass Oxy die PE-Aktivität verstärkt und Naltrexon (Nalt), ein unspezifischer Opioidantagonist, die PE-Aktivität reduziert, und zwar in einem doppelblinden, placebokontrollierten, Within-Subject fMRT-Design, das soziale Erwartungsverletzungen zur Induktion von PEs nutzt. Die Versuchspersonen (N=12) erhielten intranasales Oxy (24 IU), orales Nalt (50 mg) oder ein Placebo, bevor sie eine anstrengungsbasierte Aufgabe mit probabilistischen sozialen Ausgängen absolvierten, die darauf ausgelegt war, negative soziale PEs zu induzieren. Die ROI-Analyse zeigte eine erhöhte PE-bezogene Aktivität unter Oxytocin im rechten dorsolateralen Nucleus accumbens sowie zusätzliche Trendniveau-Erhöhungen im ventromedialen Nucleus accumbens und in der rechten basolateralen Amygdala. Eine Opioidantagonisierung durch Nalt reduzierte die PE-bezogene Aktivität nicht signifikant, mit lediglich einer Reduktion auf Trendniveau in der rechten Substantia nigra pars compacta. Entgegen der Hypothese zeigten die meisten Regionen numerisch erhöhte PE-Aktivität, und

eine Post-hoc-Analyse ergab eine signifikante Zunahme der PE-Aktivität im linken dorsolateralen Nucleus accumbens. Diese Befunde liefern vorläufige Evidenz dafür, dass Oxy salienzbezogene Komponenten der PE-Verarbeitung moduliert, während die Rolle endogener Opioide komplexer und weniger konsistent erscheint. Die Ergebnisse implizieren darüber hinaus, dass Oxy soziale Salienz nicht primär über Bottom-up-Aufmerksamkeitsmechanismen beeinflusst, wie in der ursprünglichen *Social-Saliency-Hypothese* vorgeschlagen, sondern auch durch die Modulation von PE-Signalen, was auf einen potenziellen Top-down-Beitrag zur Salienzzuweisung in sozialen Kontexten hinweist.

Abstract English

Prediction errors (PEs) encode the difference between expected and actual outcomes and thus are a fundamental component in adaptive learning. The mechanics of the PE have been extensively modelled in computational neuroscience, and there is comprehensive, albeit not conclusive, evidence on the regions involved in PE processing and their specific roles within the PE circuit. The broad modulatory function of oxytocin (Oxy) and opioids in reward processing, as well as a few initial studies, suggests that these two neuromodulators also play a crucial role in PE processing. There is a solid theoretical foundation as well as some initial empirical evidence suggesting that Oxy enhances PE activity in response to social expectation violations. The role of opioids in PE-processing has only been examined for non-social rewards; however, since opioids modulate the processing of social rewards, it is reasonable to assume that social PEs are also modulated. Consequently, the present study tests the hypothesis that Oxy amplifies PE activity and Naltrexone (Nalt), an unspecific opioid antagonist, reduces PE activity using a double-blind, placebo-controlled, within-subject fMRI design using social expectancy violations to induce PEs. The participants (N=12) received intranasal Oxy (24 IU), oral Nalt (50 mg), or a placebo before completing an effort-based task with probabilistic social outcomes, designed to induce negative social PEs. ROI analyses revealed increased PE-related activity under oxytocin in the right dorsolateral nucleus accumbens, with additional trend-level increases in the ventromedial nucleus accumbens and right basolateral amygdala. Opioid antagonism through Nalt did not reduce PE-related activity significantly, with only one trend level reduction in the right substantia nigra pars compacta. Contrary to the hypothesis, most regions showed numerically increased PE activity, and post-hoc analysis revealed a significant increase in PE activity in the left dorsolateral nucleus accumbens. These findings provide preliminary evidence that oxytocin modulates salience-related components of PE processing, while the role of endogenous opioids appears more complex and less consistent. The results further imply that Oxy may

influence social salience not primarily via bottom-up attentional mechanisms, as proposed in the original *Social Saliency Hypothesis*, but also through the modulation of PE signals, indicating a potential top-down contribution to salience assignment in social contexts.