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Effects of Oxytocin and Naltrexone on Food-Related Incentive Salience in Humans

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Oliver Erich Bichler BSc

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Betreut von | Supervisor:	Univ.-Prof. Giorgia Silani Privatdoz. PhD

Abstract

In light of rising rates of obesity and eating disorders, understanding the motivational mechanisms underlying consummatory behavior is increasingly important. One key process underlying motivation to eat is food-related incentive salience, which is defined as the motivational value attributed to food stimuli and shaped by both homeostatic and hedonic processes. Animal and clinical research suggests that oxytocin and naltrexone may reduce wanting of food rewards by targeting these regulatory systems. Accordingly, the present study examined whether single or combined administration of oxytocin and naltrexone reduces food-related incentive salience in a sample of healthy young women. For this purpose, a randomized, double-blind, placebo-controlled four-period crossover design was employed in which nineteen participants completed four experimental sessions corresponding to different drug conditions (placebo, oxytocin, naltrexone, and combined administration). During each session, wanting for high and low food rewards was assessed using subjective ratings, exerted effort, and functional magnetic resonance imaging targeting reward- and satiety-related brain regions. Contrary to expectations, neither single nor combined drug administration significantly reduced wanting ratings or exerted effort relative to placebo, and no significant drug-related differences were observed in satiety-related hypothalamic regions or mesolimbic reward-related areas. However, exploratory analyses indicated greater differentiation in wanting between high food rewards and low food rewards under combined drug administration, although this effect was not consistently reflected across behavioral and neuroimaging measures. Overall, the findings do not support robust anorexigenic effects of oxytocin or naltrexone under the present conditions and suggest that their influence on food-related motivation may depend on the individual's motivational and metabolic state.

Keywords: incentive salience, homeostatic hunger, hedonic hunger, oxytocin, naltrexone

Zusammenfassung

Angesichts der steigenden Prävalenz von Essstörungen und Adipositas kommt dem Verständnis der motivationalen Mechanismen, die unser Essverhalten steuern, eine zentrale Bedeutung zu. Nahrungsbezogene *Incentive Salience*, also der motivationale Wert, der Nahrungsreizen zugeschrieben wird, wird sowohl durch homöostatische als auch durch hedonische Prozesse beeinflusst. Tierexperimentelle und klinische Studien legen nahe, dass Oxytocin und Naltrexon das *Wanting* von Nahrungsreizen reduzieren könnten. Basierend darauf untersuchte die vorliegende Arbeit, ob die alleinige oder kombinierte Verabreichung von Oxytocin und Naltrexon die nahrungsbezogene Incentive Salience bei gesunden jungen Frauen beeinflusst. Im Rahmen eines randomisierten, doppelblinden und Placebo-kontrollierten Experiments nahmen 19 Teilnehmerinnen an vier experimentellen Sitzungen teil, in welchen das Wanting für bevorzugte und weniger bevorzugte Nahrungsreize mittels subjektiver Ratings, aufgewendeter Anstrengung sowie funktioneller Magnetresonanztomographie gemessen wurde. Die Messungen erfolgten hierbei unter alleiniger oder kombinierter Gabe von Oxytocin, Naltrexon oder Placebo. Entgegen den Erwartungen führte weder die alleinige noch die kombinierte Verabreichung der Wirkstoffe zu einer Reduktion der Wanting-Ratings oder der aufgewendeten Anstrengung im Vergleich zur Placebo Bedingung. Auch in hypothalamischen und mesolimbischen Hirnregionen, welche eine zentrale Rolle bei der Regulation von Sättigung und Belohnungsverarbeitung spielen, wurden keine signifikanten Aktivierungsunterschiede zwischen den Medikamentenbedingungen beobachtet. Explorative Analysen deuteten jedoch auf eine stärkere Differenzierung im Wanting zwischen bevorzugten und weniger bevorzugten Nahrungsreizen unter kombinierter Medikamentengabe hin. Insgesamt liefern die Ergebnisse keine Evidenz für die Existenz robuster anorexigener Effekte von Oxytocin oder Naltrexon unter den vorliegenden experimentellen Bedingungen.

Schlüsselwörter: Incentive Salience, homöostatischer Hunger, hedonischer Hunger, Oxytocin, Naltrexon

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1. Introduction

1.1 Background and Rationale

Although eating behavior may appear straightforward, it is governed by a complex interplay of physiological, psychological, and cultural factors (Dakin et al., 2024). Advancing our understanding of this multifaceted behavior is essential for public health, as it is closely linked to both obesity and eating disorders. Obesity rates are particularly high in many high- and middle-income countries, affecting up to 10% of the population and continuing to rise (Koliak et al., 2023). This trend constitutes a significant public health concern, given its association with cardiovascular disease and diabetes (Riaz et al., 2018). In parallel, the prevalence of eating disorders has reached unprecedented levels, with lifetime rates of up to 8.4% in women and 2.2% in men (Galmiche et al., 2019). Despite their clinical relevance, the underlying causes of eating disorders and overeating remain insufficiently understood (Klockars et al., 2018), underscoring the need for further research.

A key challenge in unraveling the etiology of eating-related disorders lies in comprehensively understanding the motivational factors that govern eating behavior, as both homeostatic (energy-balance driven) and non-homeostatic drives contribute in complex and still insufficiently understood ways (Berthoud & Münzberg, 2011; Hinton et al., 2004; Woods & Begg, 2016). This thesis aims to extend the existing literature by investigating how homeostatic and hedonic (pleasure- and reward-driven) mechanisms of appetite regulation interact to shape the motivation to consume specific types of food rewards. In particular, the present thesis investigates the neurobiological substrates of food motivation, focusing on the effects of well-established pharmacological agents to provide insight into the interplay between reward-related and energy-related drivers of eating behavior. Specifically, the central research question examined in this thesis concerns how oxytocin and naltrexone, administered alone and in combination, influence food-related incentive salience in humans.

1.2 Incentive Salience

A well-established framework for conceptualizing the motivational processes underlying appetite is the concept of incentive salience. Incentive salience refers to the motivational value attributed to stimuli, such as cues associated with specific rewards (Berridge, 2009). For instance, the smell of fresh pastries can make certain baked goods more desirable and trigger the motivation to acquire and consume them. This process, often described as “wanting,” is distinct from “liking,” which refers to the hedonic pleasure derived from eating (Berridge & Robbinson, 2016). Although “wanting” and “liking” frequently co-occur, they are conceptually and neurobiologically distinct: “wanting” is primarily regulated by mesolimbic

dopamine pathways, but opioid systems also contribute to both motivational and hedonic aspects of food reward (Morales & Berridge, 2020).

Importantly, incentive salience is dynamically regulated by both internal states and external cues. When the body experiences energy deficiency, the hypothalamus interacts with mesocorticolimbic pathways to enhance the incentive salience of calorie-rich foods (Morales & Berridge, 2020). Conversely, in environments abundant with palatable foods, external cues such as sight or smell can evoke strong “wanting” even in the absence of physiological hunger, potentially overriding homeostatic regulation (Bertonatti et al., 2021; Morales & Berridge, 2020). These motivational drivers can be categorized as homeostatic hunger (Cifuentes & Acosta, 2022) and hedonic hunger (Mankad & Gokhale, 2021), both of which are crucial for understanding eating motivation.

While “liking” is also a significant predictor of food motivation, this thesis will primarily focus on “wanting,” as it is more closely tied to incentive salience and appears to be a stronger predictor of food motivation overall (Morales & Berridge, 2020; Recio-Román et al., 2020). Nonetheless, the role of “liking” should not be overlooked, particularly in influencing the consumption of less palatable or less energy-dense foods (Recio-Román et al., 2020).

2. Theory

2.1 Homeostatic Hunger

Homeostatic hunger encompasses all mechanisms that connect an individual’s physiological energy requirements with the behavioral and physiological processes that ensure adequate food intake (Dakin et al., 2024). It represents the component of food-related incentive salience that arises from the conscious awareness of internal cues and bodily sensations associated with hunger and satiety (Lowe & Butryn, 2007).

Conceptually, homeostatic hunger can be understood as a complex feedback loop, integrating a range of physiological and neurochemical signals to elicit either appetite-stimulating (orexigenic) or appetite-suppressing (anorexigenic) responses. Peripheral hormones, such as leptin (anorexigenic, secreted by adipose tissue) and ghrelin (orexigenic, secreted by the stomach), play crucial roles in this feedback system by conveying the body’s energy status to the brain (Cifuentes & Acosta, 2022; Tran et al., 2022; Yanagi et al., 2018). The secretion of these hormones, as well as others like peptide YY (PYY) and cholecystokinin (CCK), is regulated by physiological states such as gastric emptiness, blood glucose levels, and fatigue, all of which reflect current energy needs (Camilleri, 2019).

These hormonal signals act primarily on the hypothalamus, particularly the arcuate nucleus (ARC), which contains distinct populations of AgRP/NPY (orexigenic) and POMC/CART (anorexigenic) neurons (Ahn et al., 2022; Sun et al., 2025). These neuron populations decode metabolic feedback, promoting either hunger or satiety, and initiate appropriate feeding behaviors (Sun et al., 2025). Furthermore, the ARC projects to other key hypothalamic regions, including the paraventricular nucleus (PVN), which coordinates eating behavior, and the lateral hypothalamic area (LHA), where hypocretin/orexin neurons integrate both homeostatic and hedonic signals (Qualls-Creekmore & Münzberg, 2018; Simpson et al., 2009).

Importantly, energy deficits enhance hypothalamic sensitivity to food cues, thereby amplifying their motivational salience through interactions with reward circuitry (Morales & Berridge, 2020). Through the illustrated mechanisms, physiological hunger states can potentiate the "wanting" responses to environmental food stimuli, thereby driving consumption.

2.2 Hedonic Hunger

Hedonic hunger describes the aspect of food-related incentive salience governed by the desire for pleasure or reward rather than by energy needs, and typically occurs in environments where palatable foods are abundantly available (Lowe & Butryn, 2007; Mankad & Gokhale, 2021). It arises in anticipation of pleasurable food stimuli and is primarily governed by the brain’s reward circuits (Lowe & Butryn, 2007). Sensory exposure to palatable foods through sight, smell, or taste is often considered the primary trigger for hedonic hunger, although internal states such as boredom or stress can also play a role (Mankad & Gokhale, 2021). The drive to consume rewarding foods can override homeostatic signals of satiety, increasing the risk of overeating and contributing to the development of obesity and other related eating disorders (Berthoud, 2012; Hall et al., 2014; Oliveira et al., 2022).

Hedonic hunger involves complex interactions between multiple brain areas associated with reward processing and motivation, mainly involving endocannabinoid, opioid, and monoamine neurotransmitters such as dopamine and serotonin (Brunerová & Andel, 2014). The mesolimbic dopamine pathway, which projects from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc), plays a key role in mediating the motivational aspects of food reward and amplifying the incentive salience of palatable food cues (Kenny, 2011; Volkow et al., 2011). The medial shell of the NAcc is often regarded as a major pleasure center of the brain, containing so-called hedonic hotspots that are associated with the “liking” component of palatable food consumption (Caref & Nicola, 2018; Le Merrer et al., 2009). Similar hedonic hotspots can be found in the ventral pallidum (Caref & Nicola, 2018; Le

Merrer et al., 2009; Winterdahl et al., 2019). Additionally, animal studies indicate that both the NAcc and the ventral pallidum facilitate the “wanting” of food by instigating approach behavior for palatable foods, even in the absence of hunger, highlighting the importance of these brain regions in generating incentive salience (Caref & Nicola, 2018; Winterdahl et al., 2019).

Furthermore, a study by Small (2010) indicates that the insular cortex is involved in processing and integrating sensory information about taste and texture, while also integrating interoceptive and metabolic feedback, potentially contributing to the appraisal of food stimuli. Another key area involved in encoding the subjective value and pleasantness attributed to certain foods is the orbitofrontal cortex, which has been found to support adaptive decision-making based on anticipated reward in primates (Kringelbach, 2004; Rolls, 2015). Additional brain regions, including the amygdala, prefrontal cortex, and hippocampus, are involved in modulating the emotional and contextual aspects of food reward, influencing the likelihood of hedonic eating in response to environmental or internal cues (Berthoud et al., 2017; Saper et al., 2002).

It is important to recognize that hedonic and homeostatic hunger should not be understood as two completely independent systems, as they are interrelated in several ways (Morales, 2022). For instance, metabolic signals can affect hedonic aspects of eating by modulating the sensitivity to reward cues (Campos et al., 2022), and the NAcc receives input from both homeostatic and hedonic circuits (Saper et al., 2002). The dynamic interaction between these two systems helps ensure that eating behavior remains flexible and adaptive, allowing environmental cues and internal states to jointly regulate food intake (Berthoud et al., 2017; Lutter & Nestler, 2009; Marinescu & Labouesse, 2024).

2.3 Oxytocin’s role in satiety and food motivation

Oxytocin is a neuropeptide hormone that fulfills a wide range of physiological and behavioral functions. It is most prominently recognized for its roles in social bonding, childbirth, and lactation (Kerem and Lawson 2021; Liu et al. 2021). This neuropeptide is predominantly synthesized in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON), though additional production occurs in peripheral tissues such as the gastrointestinal tract and bone (Kerem and Lawson 2021; Liu et al. 2021). More recently, oxytocin has been identified as a potentially important regulator of appetite, exerting some notable anorexigenic effects. Its effects seem to arise primarily from the amplification of physiological satiation signals during meals rather than from altering baseline hunger or satiety between meals (Liu et al. 2021).

To understand how oxytocin influences food-related incentive salience, it is important to consider the neural pathways through which it acts. Oxytocinergic neurons originating in the PVN project to several brain regions that are critical for feeding behavior. One key region is the arcuate nucleus (ARC) of the hypothalamus, which contains both anorexigenic POMC neurons and orexigenic NPY/AgRP neurons (Kerem and Lawson 2021). POMC neurons express oxytocin receptors. When these receptors are activated by oxytocin, the neurons increase their release of satiety-promoting signals such as alpha-MSH. This process strengthens downstream satiety mechanisms in the hypothalamus and brainstem and helps suppress appetite (Campbell et al. 2017; Sabatier et al. 2013). Oxytocinergic projections also target AgRP/NPY neurons in the ARC and can inhibit their orexigenic activity, which further promotes satiety (Biddinger et al. 2024; Sabatier et al. 2013). Studies on animals indicate that oxytocin acts within the ventromedial hypothalamus (VMH), often called the satiety center, to signal fullness and suppress food intake (Head et al. 2019; Klockars et al. 2017; Yu and Kim 2012). Oxytocin has also been shown to enhance the effects of other anorexigenic molecules, including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and alpha-melanocyte-stimulating hormone (alpha-MSH). These interactions help facilitate meal termination and amplify satiety signaling (Head et al. 2019; Liu et al. 2021). Taken together, these findings suggest that oxytocin modulates homeostatic hunger by integrating and amplifying multiple anorexigenic signals within the hypothalamus and hindbrain, supporting energy balance and homeostasis (Olszewik et al. 2022; Olszewik et al. 2010).

In addition to its primary homeostatic functions, oxytocin appears to influence food-related incentive salience by acting on reward-related brain regions. Projections from oxytocinergic neurons reach the VTA and NAcc, which are central to the brain's reward circuitry. In these regions, oxytocin modulates dopamine signaling and attenuates responses to food-predictive cues (Liu et al., 2020). These effects depend on the organism's current energy state (Hung et al. 2017). As discussed in Section 2.2, homeostatic and hedonic hunger are not entirely distinct processes. Oxytocin's modulation of reward circuits is an example of how homeostatic mechanisms can influence hedonic aspects of eating. In other words, the homeostatic component of food related incentive salience directly affects the reward-driven, hedonic dimension of food related incentive salience.

Based on the presented findings regarding the mechanisms by which oxytocin is thought to influence homeostatic and hedonic hunger, the following hypotheses were formulated:

H1: Participants receiving oxytocin will show decreased wanting of food compared to participants in the placebo condition.

H1a: Participants receiving oxytocin will show increased activation in hypothalamic regions during processing of food cues compared to participants in the placebo condition.

It is important to note that, due to the small size of the ARC, its activity cannot be reliably measured with fMRI. For this reason, this study will examine activation differences in the hypothalamus as a whole.

H1b: Participants receiving oxytocin will show decreased activation in the ventral tegmental area and the nucleus accumbens during processing of food cues, compared to participants in the placebo condition.

2.4 Naltrexone's role in satiety and food motivation

Naltrexone, a synthetic opioid receptor antagonist, is most well-known for its use in the treatment of opioid use disorder and alcohol use disorder. In these contexts, it dampens the euphoric and reinforcing effects of these substances, leading to a reduction in craving and a lower risk of relapse (Maisel et al., 2013; Ray et al., 2010). Naltrexone acts by binding to opioid receptors in the brain, primarily mu-opioid receptors, without activating them. This prevents endogenous opioids from binding to these receptor sites (Ray et al., 2010; Unterwald, 2008).

The opioid system plays a central role in regulating the reward-related properties of various stimuli, making it strongly relevant to the concept of hedonic hunger. Specifically, activation of mu-opioid receptors in the NAcc and the ventral pallidum enhances both the pleasure ("liking") and motivational value ("wanting") derived from palatable foods, thereby influencing the key components of food reward (Nathan & Bullmore, 2009; Nummenmaa et al., 2018; Peciña & Smith, 2010). This effect is largely explained by the interaction between opioids and dopamine systems within the brain's reward circuits. Opioids amplify both incentive salience and sensory pleasure by modulating dopaminergic activity. As a result, this interplay strengthens the motivation to consume palatable foods, even in the presence of satiety signals, providing a neurochemical basis for the powerful drive associated with hedonic eating (Nummenmaa et al., 2018; Nogueiras et al., 2012). Other brain areas involved in generating hedonic hunger modulated by opioids include the orbitofrontal cortex (OFC), which contains hedonic hotspots similar to those in the NAcc and ventral pallidum (Morales & Berridge, 2020), as well as the amygdala, which assigns emotional value (valence) and salience to food cues (Izadi & Radahmadi, 2022; Tiedermann, 2020).

Although less pronounced, opioids may also play a role in the regulation of homeostatic hunger to some degree (Pennock & Hentges, 2011). POMC neurons in the arcuate nucleus of the hypothalamus express μ-opioid receptors. Activation of these receptors can trigger G-protein-coupled hyperpolarization, effectively downregulating the activity of these neurons (Pennock & Hentges, 2011; Pennock & Hentges, 2014). This downregulation leads to a reduction in the release of anorexigenic peptides, such as α-MSH, which normally act to

suppress appetite and promote energy expenditure, thereby reducing satiety signaling (Pennock & Hentges, 2011; Pennock & Hentges, 20114). Conversely, blockade of μ-opioid receptors would be expected to attenuate this inhibitory effect, resulting in relatively enhanced satiety signaling compared to baseline conditions.

Given that naltrexone acts as an opioid antagonist, blocking mu-opioid receptors involved in a variety of modulatory reward-related and some homeostatic processes, it can be deduced that it should have pronounced effects on individuals' food related incentive salience. Thus, based on the presented findings, the following hypothesis were formulated:

H2: Participants receiving naltrexone will show decreased wanting of food compared to participants in the placebo condition.

H2a: Participants receiving naltrexone will show decreased activation in the nucleus accumbens and ventral pallidum during processing of food cues compared to participants in the placebo condition.

H2b: Participants administered naltrexone will show decreased activation in the amygdala during processing of food cues food cues compared to participants in the placebo condition.

2.5 Prior Research on the anorexigenic effects of oxytocin and naltrexone

In the following sections, empirical findings on the anorexigenic effects of oxytocin and naltrexone are considered, both individually and in combination, in regard to how they affect food motivation in animals and humans.

2.5.1 Prior Research on the anorexigenic effects of oxytocin

The effects of oxytocin on hunger and eating behavior have been extensively investigated. In animal models, oxytocin administration reduces food intake, primarily by enhancing satiation once eating has commenced, while its impact on the initial drive to eat appears less pronounced (Head et al., 2019; Leslie et al., 2018;).

In humans, the evidence is more nuanced. For instance, a clinical study by Zhang et al. (2013) found that intranasal oxytocin administered four times daily over eight weeks led to significant weight reduction in obese, but otherwise healthy, individuals. Oxytocin's anorexigenic effects in humans are most consistently observed in the context of hedonic eating, such as the reduction of palatable snack intake, rather than reliably decreasing food consumption driven by physiological energy needs (Lawson et al., 2015; Ott et al., 2013; Spetter et al., 2018). However, it should be noted that effects on homeostatic hunger may be more difficult to detect, as hedonic aspects of food rewards are often more salient and exert a stronger measurable influence in clinical studies (Lutter & Nestler, 2009).

Furthermore, several fMRI studies have reported that intranasal oxytocin administration reduces blood-oxygenation responses and functional connectivity in hypothalamic and reward-related brain regions during food cue processing compared with placebo, providing neuroimaging evidence consistent with oxytocin's anorexigenic effects (Plessow et al., 2018; van der Klauw et al., 2017). Additionally, it is important to note that not all studies examining the effects of oxytocin have been able to demonstrate significant anorexigenic effects. A meta-analysis conducted by Leslie et al. (2018) indicated no overall effect of oxytocin on energy intake in humans, with considerable variability depending on factors such as dose, duration of administration, population studied, and the composition of the diet.

2.5.2 Prior Research on the anorexigenic effects of naltrexone

While oxytocin seems to be involved in a variety of homeostatic and hedonic processes related to food intake, past research on the effects of naltrexone on hunger and eating behavior indicates that naltrexone primarily modulates hedonic hunger (Valbrun & Zvonarev; 2020). Studies performed on rats have demonstrated that naltrexone administration leads to a decrease in the intake of preferred, more palatable foods, while often not affecting or even increasing the consumption of standard chow (Apfelbaum & Mandenoff, 1981; Cooper & Turkish, 1989). In a study conducted by Morales et al. (2020), naltrexone administration led to a reduction in binging on sucrose and alcohol, further supporting the notion that naltrexone reduces food-related incentive salience by affecting reward-related neural pathways.

In humans, naltrexone on its own has not been shown to significantly reduce the craving for foods. However, a study by Mason et al. (2015) indicates that naltrexone weakens the association between reward-driven eating and food craving intensity, suggesting that it specifically affects the hedonic value of presented food rewards. When combined with bupropion, naltrexone has also been shown to effectively aid weight loss by reducing cravings and decreasing appetite (Wharton et al., 2025). Additionally, Murray et al reported that naltrexone not only decreased activation in reward related brain areas in reaction to chocolate, but also increased aversive-related activation to unpleasant food stimuli in the amygdala and anterior insula (Murray et al., 2014). There are no studies indicating that naltrexone on its own effectively aids weight loss (Kulak Bejda et al., 2020).

Bupropion stimulates POMC neurons, which leads to the release of alpha-MSH and beta-endorphin. Alpha-MSH signals satiety, but its effects are downregulated by beta-endorphin, which binds to the same neurons. Naltrexone blocks beta-endorphin feedback inhibition, which enhances the satiety signaling initiated by bupropion (Sherman et al., 2016). This indicates that, although naltrexone may influence the hedonic value of food rewards, it does not sufficiently affect the homeostatic components of satiety signaling. Thus, targeting both hedonic and homeostatic regulation of appetite, through the combined actions of bupropion

and naltrexone, appears necessary to meaningfully affect food motivation and actual eating behavior in humans.

2.5.3 Prior research on the combined effects of oxytocin and naltrexone

There is also evidence from animal models that the combined effects of naltrexone and oxytocin may exceed the anorexigenic effects observed when each drug is administered individually. In two experimental studies by Head et al. (2021) involving rats, the combined administration of both drugs resulted in reduced consumption of sucrose and high-fat foods, with one study additionally reporting weight loss attributable to decreased intake of palatable foods. Furthermore, in a case study involving a 13-year-old male with hypothalamic obesity, treatment with intranasal oxytocin alone led to reductions in BMI z-score and hyperphagia. The subsequent addition of oral naltrexone produced even greater and more sustained improvements in both weight and appetite control, suggesting the potential for multiplicative effects on food-related incentive salience when both drugs are combined (Hsu et al., 2018).

As previously noted, POMC neurons express oxytocin receptors, and activation of these receptors increases the release of alpha-MSH, a peptide involved in satiety signaling. Naltrexone can also act on these neurons by inhibiting the autoinhibitory feedback mediated by beta-endorphin, thereby enhancing oxytocin-induced satiety signaling and indirectly modulating homeostatic hunger, in a manner similar to the interaction between naltrexone and bupropion. Additionally, as discussed in Sections 2.3 and 2.4, naltrexone's reduction of the hedonic value of food operates through neural pathways partially distinct from those involved in oxytocin's modulation of homeostatic and hedonic hunger, further supporting the potential for complementary anorexigenic effects.

Taken together, these findings lead to the following hypothesis:

H3: Participants receiving both naltrexone and oxytocin will show decreased wanting of food compared to participants in the placebo condition.

H4: Participants receiving both naltrexone and oxytocin will show decreased wanting of food compared to participants given only oxytocin.

H5: Participants receiving both naltrexone and oxytocin will show decreased wanting of food compared to participants given only naltrexone.

Furthermore, the combined administration of both agents is expected to produce complementary effects, resulting in greater activation differences in specific brain regions compared to single-drug conditions. More specifically, based on previous research on the individual effects of each drug, I predict the following:

H4a: Participants receiving both oxytocin and naltrexone will show increased activation in hypothalamic regions involved in satiety compared to participants given only oxytocin.

H5a: Participants receiving both oxytocin and naltrexone will show decreased activation of the nucleus accumbens and ventral pallidum in response to food cues, compared to participants given only naltrexone.

2.6 Investigating mechanistic differences between oxytocin and naltrexone

In addition to examining the anorexigenic effects of oxytocin and naltrexone, this study also aims to further investigate the distinct mechanisms by which each drug exerts its effects. As highlighted in the previously reviewed literature, oxytocin may influence food-related incentive salience by modulating both homeostatic and hedonic processes, whereas naltrexone appears to primarily affect hedonic pathways. However, studies testing these assertions have produced mixed results, underscoring the need for further research in this area. If oxytocin influences both homeostatic and hedonic processes while naltrexone primarily affects hedonic pathways, then naltrexone's anorexigenic effects on less preferred foods should be weaker than those of oxytocin, which is expected to reduce wanting of both highly desired and less preferred food rewards. Based on this, I predict the following:

H6: The difference in wanting between preferred and non-preferred food rewards will be larger in participants administered oxytocin compared to those given naltrexone.

3. Method

3.1 Sample Size

Sample size planning was conducted using G*Power (version 3.1.9.7). Because direct power estimation for linear mixed models is not straightforward in standard power analysis software, an approximation based on repeated-measures comparisons was used to guide sample size decisions. Given the partially conflicting literature on the anorexigenic effects of oxytocin and naltrexone (see Section 2.5), a small-to-medium effect size was assumed ($d = 0.4$). Participants completed four sessions with distinct experimental conditions, allowing within-subject comparisons across drug conditions. Based on this approximation ($d = 0.4$, $\beta = 0.2$, $\alpha = 0.05$), a minimum of 51 participants was estimated to achieve adequate statistical power. Due to time constraints, however, only 19 participants were tested behaviorally. Additionally, three participants were excluded from the fMRI analysis due to technical issues, resulting in a final sample of 16 participants for the neuroimaging analyses

The sample consisted exclusively of female participants, as the broader project included only women. Inclusion criteria included right-handedness, heterosexual orientation, absence of

substance abuse as well as psychiatric or neurological disorders, non-pregnancy, and no contraindications for pharmacological or fMRI testing. Ethical approval for research involving the combined administration of oxytocin and naltrexone had already been granted by the relevant ethics committee (EK 1393/2017). Data acquisition and recording adhered to the ethical principles for medical research involving human subjects as outlined in the Declaration of Helsinki.

3.2 Stimuli

Food rewards consisted of three different types of dairy products: chocolate milk, a mixture of milk and chocolate milk (in a 4:1 ratio), and plain milk. All three types of food reward were matched for fat and sugar content (1.5 g fat and 10 g sugar per 100 g), minimizing potential differences in macronutrient composition so that the rewards primarily differed in their sensory characteristics. The temperature of the food rewards was maintained at approximately 4°C prior to administration.

Food delivery was managed using computer-controlled pumps (PHD Ultra pumps, Harvard Apparatus) connected to plastic tubes (internal diameter 1.6 mm; external diameter 3.2 mm; Tygon tubing, U.S. Plastic Corp.). Adjustable mouthpieces were attached to the tubes to ensure optimal comfort for participants during administration. For each trial, 2 mL of the designated liquid was delivered over a period of 2 seconds. Following each trial, 2 mL of tap water was administered to rinse the mouth. Over the course of the procedure, participants consumed a total of 98 mL of water and 98 mL of the various food rewards, resulting in an overall liquid intake of 196 mL.

3.3 Procedure

The following procedures were conducted at the Department of Psychiatry and Psychotherapy, Medical University of Vienna. A randomized, double-blind, placebo-controlled, four-period crossover design was used to ensure that each participant experienced all conditions in a random order across four separate sessions, allowing for direct comparison of drug effects within the same individuals while controlling for period and carryover effects.

Before participating in the experiment, all individuals underwent an initial health screening at the lab. During the four subsequent visits, participants received nasal and oral drugs in four different conditions, each administered once in a randomized order determined by a four-period, four-treatment Latin square method (ACDB, BDCA, CBAD, DABC in a 4:4:4:4 ratio). Participants attended each session with an empty stomach. Upon arrival, a urine drug test (screening for opiates, amphetamines, methamphetamine, and cocaine) and a pregnancy

test were conducted. Afterwards, participants completed safety questionnaires and received instructions regarding the procedure.

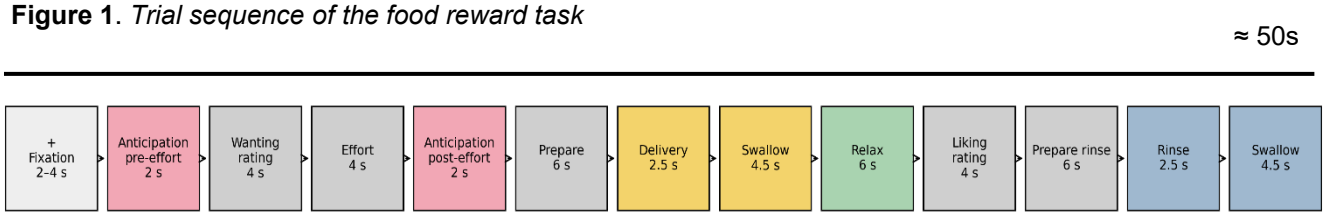
Following the initial screening, participants were administered either 50 mg of naltrexone (Dependex, opioid antagonist) or 650 mg of mannitol (placebo). Twenty minutes after capsule ingestion, 24 IU of oxytocin (Syntocinon, Novartis) or saline placebo (0.9%, Miwana) was administered intranasally. The main procedure began 20 minutes after the second drug administration, a timeframe chosen to maximize the concentrations of all administered drugs during the subsequent tasks (Gossen et al., 2014; Vereby et al., 1976). The main experimental procedure consisted of the administration of different food and social rewards and measured both wanting and liking of the administered rewards. As this study was part of a larger project examining the effects of oxytocin on social rewards and liking, the following description focused on aspects relevant to this study, specifically the administration of food rewards and the measurement of wanting.

After participants entered the fMRI scanner, each type of food reward was administered once and rated for liking on a scale from “not at all” to “very much”. In the main experiment, the most liked liquid served as the "high reward," the second most liked as the "low reward," and pure milk consistently as the "very low reward." This approach accounted for interpersonal variation, although it was expected that most participants would find sweeter solutions more rewarding. Wanting was measured both subjectively, via ratings on a scale from “not at all” to “very much”, and behaviorally, via the force exerted on a hand dynamometer. Maximum voluntary effort was measured immediately before the task by asking participants to squeeze the dynamometer with their right hand as hard as possible three times for three seconds each. The main experimental procedure consisted of four blocks, each with 16 trials. Food rewards were administered in half of the blocks, while the remaining blocks were not relevant to this study. Blocks were presented in an interleaved, counterbalanced order (ABAB or BABA) across participants.

Each trial began with a 2-second presentation of a picture announcing the potential food reward, which could be either high or low. This was followed by a wanting rating phase lasting up to 4 seconds, during which participants indicated their desire for the announced reward. Next, participants performed a 4-second period of physical effort by squeezing a hand dynamometer with their right hand. The amount of force exerted determined the probability of receiving the announced reward, with visual feedback provided throughout. A 2-second picture then displayed the actual reward obtained, which could be high, low, or very low, if insufficient effort was made. Participants then had 6 seconds to prepare for reward delivery, followed by 7 seconds during which the food reward was delivered. After receiving the reward, there was a 6-second relaxation phase, and participants subsequently rated their

liking of the received food on a continuous scale for 4 seconds. Each trial concluded with a 5-second preparation phase for mouth rinsing, immediately followed by a 7-second rinsing period before the next trial began. After each block, participants were allowed a short break. A visual representation of the trial sequence is shown in Figure 1. The tasks were run on a Windows 10 computer using MATLAB with the Cogent 2000 and Cogent Graphics toolboxes and presented on an MR-compatible monitor viewed via a mirror system.

Figure 1. *Trial sequence of the food reward task*



3.4 Analysis

3.4.1 Analysis of behavioral data

Statistical analyses of behavioral data were conducted using JASP (version 0.19.3.0). Descriptive statistics (means and standard deviations) were calculated for the dependent variable wanting, assessed via both subjective self-report ratings and objective hand-pressure task performance for each drug condition.

Differences in wanting ratings and exerted effort were tested using linear mixed models, which controlled for session order, included subjects as a random intercept to account for repeated measures and independence of observations, and modeled the trial-level data. Post hoc tests were performed to compare drug conditions in accordance with Hypotheses H1 through H5. Additionally, difference scores (wanting for high versus low rewards) were computed for each participant and analyzed using a second linear mixed model, also controlling for session order, and including subjects as random intercepts. Hypothesis H6 was assessed via a post hoc comparison of the estimated difference between the naltrexone and oxytocin conditions.

Model assumptions were evaluated by inspecting residuals and Q-Q plots to assess normality and homoscedasticity. Although extreme values were noted, they were retained in the analyses, as they reflect the naturally high variability in wanting measures. Type I error due to multiple pairwise comparisons was controlled using Bonferroni corrections where appropriate. Data were checked for completeness.

3.4.2 Analysis of fMRI data

All fMRI data were analyzed using the Statistical Parametric Mapping software package (SPM12; Wellcome Trust Centre for Neuroimaging, UCL, London, UK) implemented in MATLAB (The MathWorks Inc., Natick, MA).

Preprocessing included slice timing correction, spatial realignment, head motion correction, normalization to MNI space, and spatial smoothing. A preprocessing pipeline combining FSL and ANTs routines, optimized for 7T fMRI data, was applied (Sladky et al., 2018). This pipeline achieved high image quality following transformation to MNI space (Sladky et al., 2018). Datasets were additionally corrected for physiological artifacts, and distortion correction was performed using phase images acquired immediately after functional scans (Windischberger et al., 2004).

For first-level analysis, a general linear model was constructed for each participant to model BOLD responses to different food cues, specifically comparing reward announcement against fixation cross. Group-level analyses for hypotheses concerning neural activation involved repeated-measures t-tests comparing relevant conditions within participants for the predefined ROIs (see Section 2 for ROI definitions).

Whole-brain analyses were conducted to explore potential drug effects throughout the brain. For each pairwise drug comparison, voxel-wise repeated-measures t-tests were performed to identify regions showing significant differences in BOLD responses to food cues. This exploratory approach was conducted to identify potential unanticipated drug effects in brain regions outside the predefined ROIs. Correction for multiple comparisons was applied using family-wise error correction where applicable.

4. Results

4.1 Descriptive Statistics

Descriptive statistics for wanting ratings across drug conditions and reward announcement types are shown in Table 1. Across all drug conditions, mean wanting ratings for announced high rewards were higher than for announced low rewards, indicating a successful manipulation of reward magnitude. Mean wanting ratings were comparable across drug conditions, with no indication of floor or ceiling effects. Furthermore, relatively high standard deviations were observed, indicating pronounced interindividual variability. Descriptive mean wanting ratings were highest when both drugs were administered (Mean = 35.71) and lowest in the placebo condition (Mean = 25.75). Descriptive drug effects on wanting were small compared to within-subject variability.

Measured exerted effort showed a similar pattern to the observed wanting ratings, with higher exerted effort for high-reward announcements than for low-reward announcements across all drug conditions (see Table 2). Moreover, relative variability in exerted effort was smaller than that observed for wanting ratings but remained substantial relative to the mean differences between conditions. The highest exerted effort was observed when both drugs were administered (Mean = 67.45) , and the lowest when only oxytocin was administered (55.07).

Table 1

Descriptive statistics for average wanting ratings across drug conditions and reward types

Drug Condition	Reward Announcement	N	Mean	SD
Oxy	High	19	48.48	43.56
	Low	19	9.00	39.39
	Average	19	28.74	37.50
Nal	High	19	41.60	44.02
	Low	19	15.66	39.87
	Average	19	28.63	38.47
Oxy+Nal	High	19	58.42	36.51
	Low	19	13.00	32.60
	Average	19	35.71	29.24
Pla	High	19	40.35	52.23
	Low	19	11.16	43.37
	Average	19	25.75	32.27

Note. N = 19. Oxy = oxytocin; Nal = naltrexone; Pla = placebo

Table 2

Descriptive statistics for average exerted effort across drug conditions and reward types

Drug Condition	Reward Announcement	N	Mean	SD
Oxy	High	19	60.10	22.88
	Low	19	50.04	21.06
	Average	19	55.07	20.71
Nal	High	19	66.42	24.17
	Low	19	55.77	20.19
	Average	19	61.10	20.83
Oxy+Nal	High	19	74.12	22.25
	Low	19	60.78	20.02
	Average	19	67.45	19.64
Pla	High	19	61.10	30.52
	Low	19	10.65	22.56
	Average	19	58.84	25.57

Note. N = 19. Oxy = oxytocin; Nal = naltrexone; Pla = placebo

4.2 Behavioral Analysis

To test for differences in wanting ratings and exerted effort while controlling for session order and within-subject variability, linear mixed models with random intercepts for participants were computed (see Table 3). For wanting ratings, the model showed no significant main effect of drug ($F = 0.83$; $p = 0.48$) and no significant effect of session ($F = 2.16$; $p = 0.11$). For exerted effort, no significant effects of drug ($F = 1.90$; $p = 0.14$) or session ($F = 0.11$, $p = 0.96$) were observed.

Post hoc comparisons between individual drug conditions testing hypotheses H1 to H5 were not significant for either wanting ratings or exerted effort (see Table 4 and Table 5) after Bonferroni correction for multiple comparisons. Estimated effect sizes were predominantly small. A medium-sized effect emerged for exerted effort when contrasting naltrexone and oxytocin with placebo ($d = 0.64$).

Table 3

Linear mixed-effects model examining the effects of drug condition and session order on wanting ratings and exerted effort

Effect	df_1	df_2	*F*	*p*
Wanting Ratings				
Drug	3	51	0.83	0.48
Session	3	51	2.16	0.11
Exerted Effort				
Drug	3	51	1.90	0.14
Session	3	51	0.11	0.96

Note. N = 19; *$p < 0.05$; df_1 = numerator degrees of freedom; df_2 = denominator degrees of freedom (Satterthwaite approximation). Drug condition and session were included as fixed effects. Subjects were included as a random intercept.

Table 4

Pairwise comparisons of wanting ratings across experimental conditions, controlling for the order of experimental conditions

Experimental Condition	Mean Difference	*t*	df	*p*	Cohen's d
Oxy vs Pla	2.18	0.30	51	1.00	0.09
Nal vs Pla	5.24	0.71	51	1.00	0.20
Oxy+Nal vs Pla	11.21	1.56	51	0.63	0.44
Oxy+Nal vs Oxy	9.03	1.02	51	1.00	0.30
Oxy+Nal vs Nal	5.97	0.87	51	1.00	0.24

Note. N = 19. Oxy = oxytocin; Nal = naltrexone; Pla = placebo. All pairwise comparisons were conducted as post hoc contrasts of a linear mixed-effects model with random intercepts for subjects. Session order was included as a covariate. *p*-values were adjusted using Bonferroni correction. Cohen's d values were approximated from contrast t-statistics.

Table 5

Pairwise comparisons of exerted effort across experimental conditions, controlling for the order of experimental conditions

Experimental Condition	Mean Difference	*t*	df	*p*	Cohen's d
Oxy vs Pla	-4.05	-0.80	51	1.00	−0.22
Nal vs Pla	3.31	0.63	51	1.00	0.18
Oxy+Nal vs Pla	9.33	1.84	51	0.36	0.52
Oxy+Nal vs Oxy	13.39	2.30	51	0.13	0.64
Oxy+Nal vs Nal	6.02	1.24	51	1.00	0.35

Note. N = 19. Oxy = oxytocin; Nal = naltrexone; Pla = placebo. All pairwise comparisons were conducted as post hoc contrasts of a linear mixed-effects model with random intercepts for subjects. Session order was included as a covariate. *p*-values were adjusted using Bonferroni correction. Cohen's d values were approximated from contrast t-statistics.

To examine drug-related differences in mean difference scores for wanting ratings and exerted effort, an additional linear mixed model was conducted (see Table 6). For wanting difference scores, the model revealed a significant main effect of drug (F = 3.12, p = 0.03) and a significant effect of session (F = 3.75; p = 0.02). For exerted effort difference scores, no significant effects of drug (F = 2.65;p = 0.06) or session (F = 2.47; p = 0.07) were found.

Table 6

Linear mixed-effects model examining the effects of drug condition and session order on difference scores in wanting ratings and exerted effort

Effect	df_1	df_2	*F*	*p*
Wanting Ratings				
Drug	3	51	3.75	*.02
Session	3	51	3.12	*.03
Exerted Effort				
Drug	3	51	2.65	0.06
Session	3	51	2.47	0.07

Note. N = 19; *$p < 0.05$; df_1 = numerator degrees of freedom; df_2 = denominator degrees of freedom (Satterthwaite approximation). Drug condition and session were included as fixed effects. Subjects were included as a random intercept.

Post hoc tests comparing naltrexone and oxytocin with respect to mean difference scores for wanting ratings revealed no significant differences between drug conditions for either wanting ratings (p = 0.87) or exerted effort (p = 0.20) (see Table 7). Because a significant main effect of drug was observed, additional exploratory pairwise comparisons were conducted to further examine differences between conditions (see Table 8). These analyses revealed that the combined oxytocin and naltrexone condition exhibited a significantly larger difference between high and low food reward wanting compared to placebo.

Table 7

Pairwise comparison of mean difference scores in wanting ratings and exerted effort between naltrexone and oxytocin (oxytocin > naltrexone), controlling for the order of experimental conditions

Dependent variable	Mean Difference	*t*	df	*p*	Cohen's d
Wanting ratings	-1.53	-0.17	51	0.87	-0.05
Exerted Effort	-6.75	-1.30	51	0.20	-0.36

Note. N = 19. Difference scores reflect reward-announcement-dependent differences in wanting ratings and exerted effort (high reward announcement - low reward announcement). Contrast order Both pairwise comparisons were conducted as post hoc contrasts of a linear mixed-effects model with random intercepts for subjects. Session order was included as a covariate. Cohen's d values were approximated from contrast t-statistics.

Table 8

Exploratory pairwise comparison of mean difference scores in between drug conditions, controlling for the order of experimental conditions

Experimental Condition	Mean Difference	*t*	df	*p*	Cohen's d
Oxy vs Pla	2.40	0.30	51	0.99	0.07
Nal vs Pla	3.94	0.48	51	0.96	0.11
Oxy+Nal vs Pla	23.81	3.00	51	*.02	0.69
Oxy+Nal vs Oxy	9.12	2.62	51	0.10	0.60
Oxy+Nal vs Nal	19.87	0.87	51	0.06	0.20

Note. N = 19; *p < 0.05; Oxy = oxytocin; Nal = naltrexone; Pla = placebo. All pairwise comparisons were conducted as post hoc contrasts of a linear mixed-effects model with random intercepts for subjects. Session order was included as a covariate. p-values were adjusted using Bonferroni correction. Cohen's d values were derived from the contrast t-statistics.

4.3 FMRI Analysis

Second-level analyses of the predefined ROIs (see section 2) revealed no significant drug-related differences in BOLD activation within any of the examined regions. No activations survived FWE correction for multiple comparisons across all tested contrasts and ROIs (see Table 9). Given the absence of significant effects in the hypothesis-driven ROI analyses, descriptive reporting of peak activations without statistical thresholding was conducted to characterize potential drug-related activation patterns. As shown in Table 9, peak activations varied across hypothalamic, striatal, and limbic ROIs without a consistent pattern across contrasts. Descriptively, higher peak t-values were observed in hypothalamic regions for the combined oxytocin and naltrexone condition compared to oxytocin alone. These effects did not reach statistical significance and should therefore be interpreted cautiously.

Table 9

Exploratory peak statistics from small volume corrected ROI analyses

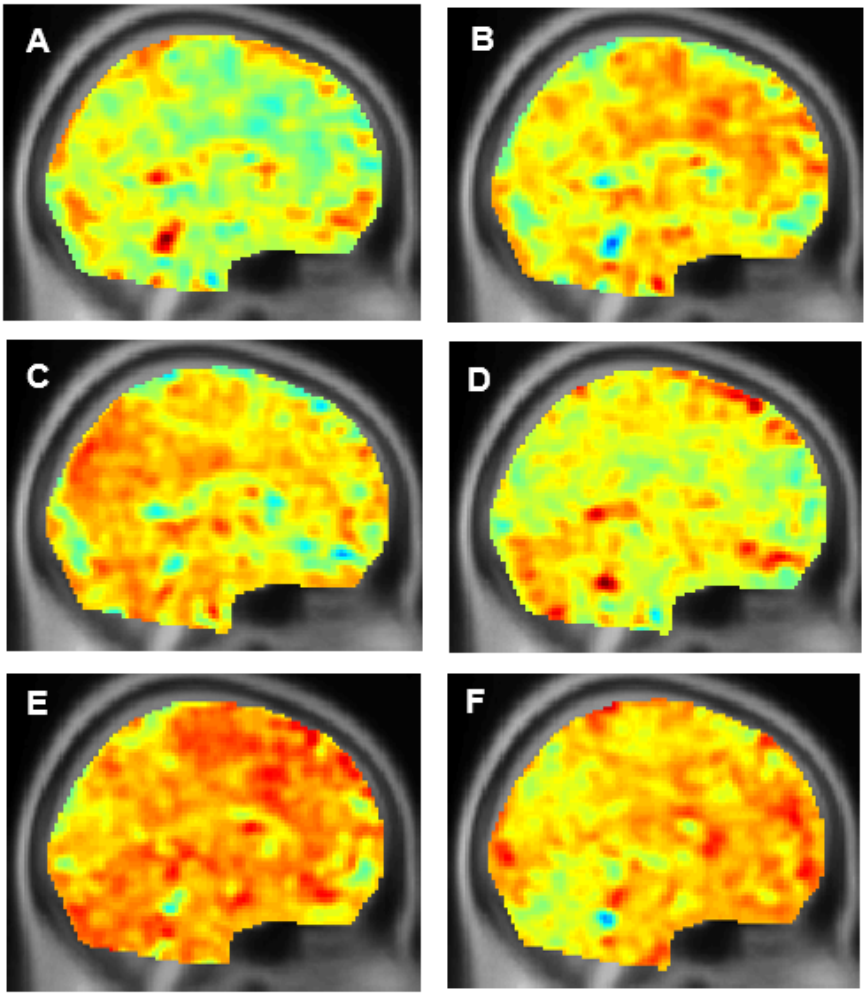
Contrasts	ROI	*t*	$p_{(uncorr)}$	MNI
Oxy vs Pla	Hypo	2.61	0.01	10 -8 -2
Oxy vs Pla	NAcc	-1.49	0.07	4 6 -6
Oxy vs Pla	VTA	-2.49	0.01	-14 -8 -10
Nal vs Pla	NAcc	-0.50	0.27	-10 10 -12
Nal vs Pla	VP	-2.58	0.01	12 -2 -2
Nal vs Pla	Amyg	-2.61	0.01	30 4 18
Oxy+Nal vs Oxy	Hypo	4.15	0.00	-12 -18 -14
Oxy+Nal vs Nal	NAcc	-0.98	0.16	-14 6 -8
Oxy+Nal vs Nal	VP	-2.07	0.03	-16 -4 -8

Note. N = 16; p = 1.0, unthresholded. Oxy = oxytocin; Nal = naltrexone; Pla = placebo.
Hypo = hypothalamus; NAcc = nucleus accumbens; VP = ventral pallidum; Amyg = amygdala; VTA = ventral tegmental area. Oxy = oxytocin; Nal = naltrexone; Pla = placebo.
$p_{(uncorr)}$ = uncorrected p-values. Positive t-values indicate greater activation in first condition (e.g., Oxy vs Pla = oxytocin > placebo). Results are exploratory and reported for descriptive purposes.

In addition to ROI-based analyses, exploratory whole brain analyses were conducted using unthresholded statistical maps for all defined contrasts of interest (see Figure 2). These analyses were performed for descriptive purposes and were not subjected to statistical thresholding or correction for multiple comparisons. As shown in Figure 2, the resulting maps revealed diffuse and spatially widespread t-value distributions without clearly delineated or

focal clusters. Across all six contrasts, the spatial patterns of positive and negative t-values were largely heterogeneous, with no contrast showing a consistent, anatomically restricted peak pattern. Visual inspection did not suggest systematic differences between oxytocin and placebo or between naltrexone and placebo, nor did it reveal more coherent activation pattern for the combined treatment relative to the single-drug conditions.

Figure 2. *Exploratory unthresholded second-level activation maps for six contrasts of interest, displayed on an axial view*



Note. No statistical threshold was applied; maps are shown for descriptive visualization only and were not used for formal hypothesis testing. Colors represent t-values (warmer colors indicate higher relative activation, cooler colors indicate lower relative activation). Panels correspond to the following contrasts: (A) Oxytocin > Placebo; (B) Oxytocin < Placebo; (C) Naltrexone < Placebo; (D) Combined treatment < Placebo; (E) Combined treatment < Oxytocin; (F) Combined treatment < Naltrexone.

5. Discussion

5.1 Summary of findings

The present thesis investigated the effects of oxytocin and naltrexone, administered alone and in combination, on food-related incentive salience in healthy young women. To address this research aim, a placebo-controlled, double-blind design was employed. Wanting was operationalized through subjective ratings and exerted effort, and functional neuroimaging was used to assess drug-related activation differences in reward- and satiety-related brain regions.

Behavioral measures of wanting did not reveal significant drug effects for either subjective wanting ratings or exerted effort. On a descriptive level, mean wanting scores were slightly higher when one or both drugs were administered compared to placebo or single-drug conditions (see Table 1), which contrasts with the hypothesized anorexigenic direction of effects.

Difference scores reflecting high versus low reward wanting indicated a modest main effect of drug and session order for wanting ratings. A comparable effect was not observed for exerted effort, although estimates pointed in a similar direction (see Table 6). Post hoc comparisons between naltrexone and oxytocin were not significant, suggesting insufficient evidence that the difference between the wanting of high food rewards compared to low food rewards is lower in the naltrexone condition, thus not supporting the claim that naltrexone affects hedonic hunger more strongly than oxytocin. However, exploratory findings suggest that the combined administration of oxytocin and naltrexone may be associated with greater differentiation in wanting of preferred vs less preferred food rewards, which could reflect additive modulation of hedonic aspects of food-related incentive salience.

FMRI analyses of predefined regions of interest including the hypothalamus, nucleus accumbens, ventral pallidum, and amygdala did not reveal significant drug-related BOLD signal changes after correction for multiple comparisons. Descriptive trends indicated slightly higher activation in satiety-related regions when comparing the combined drug condition with oxytocin alone (peak $t = 4.15$). However, these observations remain exploratory and must be interpreted cautiously in the absence of statistical significance. Exploratory second-level analyses suggested a greater number of apparent activational differences under combined drug administration compared to single-drug conditions. Nevertheless, no coherent or regionally specific pattern emerged within mesolimbic dopamine pathways or hypothalamic circuits, suggesting that the observed trends do not provide clear neural support for a systematic modulation of reward- or satiety-related processing.

Taken together, the findings do not support the hypothesis that single or combined administration of oxytocin and naltrexone produces anorexigenic effects through reduced incentive salience for food rewards. While some results hinted at drug-related influences on the differentiation between high and low reward food wanting, the present data provide insufficient evidence that naltrexone reliably enhances this distinction.

5.2 Absence of drug-induced effects on food-related incentive salience

The lack of statistically significant behavioral effects, as well as the direction of the observed descriptive trends, raises important questions regarding the translation of pharmacological modulation of food-related incentive salience from animal models to non-clinical human populations. As discussed in Section 2.5, prior findings on the anorexigenic effects of oxytocin and naltrexone are mixed and appear to show specificity to certain populations and contexts. Considering this, the drug effects examined in the present study may be highly context dependent and potentially detectable only under specific physiological or motivational conditions. Furthermore, the neural pathways through which both agents exert their effects are complex and involve distributed regulatory systems. It is therefore possible that oxytocin and naltrexone influence food-related incentive salience through mechanisms that differ from those specified in this study. While the present thesis focused on wanting as an index of incentive salience, anorexigenic effects may occur through alternative processes that were not directly assessed.

5.2.1 Oxytocin and food-related incentive salience

In animal studies as well as in selected human studies, oxytocin has been shown to produce anorexigenic effects primarily by promoting earlier meal termination (Head et al., 2019; Hsu et al., 2018; Leslie et al., 2018). As food-related incentive salience in this thesis was measured indirectly through subjective wanting ratings and exerted effort rather than through direct measures of food intake, such effects may not have been detectable using the employed methodology. Moreover, oxytocin-induced earlier meal termination in rodents suggests that its anorexigenic effects may become more pronounced once food consumption has already begun. In the present study, participants consumed only small quantities of the food rewards in short intervals, which may have limited the detectability of effects occurring during sustained meal consumption.

Additionally, there is evidence that oxytocin’s effects on food-related incentive salience are influenced by the organism’s current energy state. For example, oxytocin receptor density in satiety-related brain regions has been shown to vary in mice depending on energy needs (Head et al., 2019). Variability in participants’ metabolic state or subjective hunger levels may therefore have affected individual susceptibility to potential anorexigenic effects of oxytocin.

In a healthy sample with intact homeostatic regulation, such effects may have been subtle and difficult to detect at the behavioral level.

5.2.2 Naltrexone and food-related incentive salience

As discussed in section 2.4, naltrexone was hypothesized to affect food-related incentive salience indirectly by blocking opioid receptors that enhance the sensory pleasure and motivational salience of food rewards (Nathan & Bullmore, 2009; Nummenmaa et al., 2018; Peciña & Smith, 2010). The absence of significant effects of naltrexone on food-related incentive salience is consistent with prior research examining its role in supporting weight loss in humans (Kulak Bejda et al., 2020). However, this does not fully explain why neither behavioral nor neuroimaging results indicated reductions in participants' appraisal of the rewarding properties of food, as blockade of mu-opioid receptors in mesolimbic regions would be expected to influence reward processing (Nummenmaa et al., 2018). One possible explanation is that mu-opioid receptor antagonism does not uniformly diminish the rewarding properties of palatable foods but may instead exert more subtle and context-dependent effects. Previous research suggests that naltrexone could reduce the hedonic value of food by weakening the association between craving intensity and reward-driven eating in obese women (Mason et al., 2015). This may indicate that its effects on incentive salience are more pronounced in individuals with heightened reward sensitivity or dysregulated eating behavior, rather than in healthy populations without clinically relevant alterations in food reward processing.

Furthermore, if naltrexone reduces food-related incentive salience primarily by attenuating the link between craving and reward-driven behavior, its effects would not necessarily be expected in the absence of strong craving. Although the food rewards administered in this study were generally expected to be pleasant or neutral, it is possible that they did not necessarily induce high-intensity craving. Additionally, the noisy, unfamiliar, and potentially uncomfortable fMRI environment may have further dampened the intrinsic motivation to consume. Taken together, these factors may help explain why naltrexone did not produce measurable effects on food-related incentive salience in the present study.

Difference scores reflecting high versus low reward wanting indicated a modest main effect of drug and session order for wanting ratings. A comparable effect was not observed for exerted effort, although estimates pointed in a similar direction (see Table 6). Post hoc comparisons between naltrexone and oxytocin were not significant, suggesting insufficient evidence that naltrexone decreases hedonic hunger more strongly than oxytocin. However, exploratory findings suggest that the combined administration of oxytocin and naltrexone may be associated with greater differentiation in wanting between preferred and less

preferred food rewards, which could reflect additive modulation of hedonic aspects of food-related incentive salience.

In a healthy population, the motivational distinction between moderately pleasant stimuli may not depend on mu-opioid receptor activity as strongly as originally proposed. Furthermore, the present study employed food rewards that differed in taste but not in macronutrient composition. This contrasts with experimental paradigms in which reward options differ substantially in macronutrient content or energy density, such as comparisons of sucrose- and high-fat foods, where opioid-related modulation of highly palatable intake has been demonstrated (Apfelbaum & Mandenoff, 1981; Head et al., 2021). It may therefore be that opioid-dependent modulation of reward processing becomes more pronounced when stimuli are both highly palatable and energy-dense, conditions that are more likely to elicit strong craving responses. Under the comparatively moderate reward contrast employed in the present study, such mechanisms may not have been sufficiently engaged to produce measurable differences in reward differentiation.

5.2.3 Descriptive trends in wanting under combined administration

As neither drug alone produced a consistent descriptive reduction in food-related incentive salience, the absence of a more pronounced attenuation under combined administration is consistent with the single-drug findings. Descriptive trends suggested the opposite pattern for subjective wanting ratings, with higher ratings observed under both single and combined drug administration compared to placebo, a tendency that was generally reflected in exerted effort as well, aside from a slight opposite trend under oxytocin alone. While these findings only showed on a descriptive level, they may reflect context-dependent modulation of attention and reward processing rather than a robust enhancement of incentive salience. For instance, when examining the influence of oxytocin on attentional bias to food images in women with bulimia nervosa or binge eating disorder, oxytocin was found to enhance vigilance towards palatable food (Leslie et al., 2020). Increased attention towards announced food rewards could heighten the subjective salience of the stimuli and thereby influence wanting ratings. In contrast, any potential contribution of naltrexone to these trends is difficult to interpret, as current literature generally describes its effects as dampening reward-related processes, with no clear indication that it enhances incentive salience under specific conditions. Taken together, the observed descriptive patterns suggest that naltrexone and oxytocin may not exert simple additive effects on food-related incentive salience but could interact in complex and potentially non-linear ways that are not fully captured by the present design. However, given the absence of statistically significant effects and the inconsistency of the observed trends, these interpretations remain highly speculative.

5.3 Combined effects of oxytocin and naltrexone on reward differentiation

Interestingly, exploratory post hoc analyses indicated that the combined drug administration condition exhibited a significantly larger difference between the wanting of preferred and less preferred food rewards compared to placebo. This effect was specific to the combined administration of naltrexone and oxytocin and did not occur when comparing single-drug conditions to placebo conditions. This finding indicates that the combined administration of oxytocin and naltrexone may produce additive effects that potentially increase the wanting of palatable foods or lead to a stronger differentiation in wanting of high vs low food rewards. This directly contradicts prior findings on the anorexigenic effects of naltrexone and oxytocin in prior studies (Head et al. 2021; Hsu et al., 2018) and thus warrants further research. It must, however, be noted that similar effects or even descriptive trends were not observed for exerted effort, which limits the robustness of these findings. Furthermore, the conducted fMRI analyses did not reveal evidence for specific effects of either oxytocin or naltrexone in the NAcc or the VTA, suggesting that such effects may operate through neural mechanisms other than those examined in this study.

5.4 Theoretical implications

While the present findings do not directly support anorexigenic effects of oxytocin and naltrexone on food-related incentive salience, they nevertheless carry important theoretical implications for the study of pharmacological appetite regulation. The absence of reduced wanting following drug administration, particularly in contrast to animal and clinical studies that typically assess observable eating behavior such as food intake or weight change, suggests that oxytocin and naltrexone may not substantially alter overall food motivation in healthy populations under the present conditions. At the same time, the exploratory finding that combined drug administration increased the differentiation in wanting between higher and lower reward foods points to a modulation of reward-specific motivational processes rather than a uniform suppression of incentive salience. Such modulation, however, may not have been sufficiently strong to produce an overall reduction in wanting for food rewards. Notably, in contrast to pharmacological interventions that exert combined effects on hedonic hunger and homeostatic hunger, such as the previously discussed combined administration of naltrexone and bupropion (Sherman et al., 2016), the present findings showed no evidence of homeostatic modulation. Taken together, these findings suggest that effective pharmacological regulation of food-related incentive salience may require concurrent modulation of both homeostatic and hedonic regulatory pathways.

Additionally, the present findings suggest that pharmacological modulation of food-related incentive salience may be strongly state-dependent. Rather than producing uniform reductions in food-related wanting, drug effects may primarily emerge when motivational and

reward systems are strongly engaged, such as under conditions of heightened craving or elevated reward sensitivity. The absence of overall reductions in wanting in the present study, despite indications of more selective modulation of reward-specific motivation, is consistent with this interpretation. This pattern suggests that the examined appetite-regulating agents may not directly suppress baseline motivational drive but instead alter the gain or responsiveness of neural systems underlying incentive salience. This interpretation aligns with findings from clinical populations characterized by dysregulated reward processing, in which pharmacological interventions have been associated with measurable changes in eating behavior or weight regulation (e.g., Hsu et al., 2018; Mason et al., 2015). Accordingly, the behavioral impact of such pharmacological interventions may depend on the organism's current motivational state.

5.5 Limitations

Only 19 participants were tested in this study, which limits statistical power, even though the within-subject design increased sensitivity for the conducted analyses. This is particularly relevant given the high variability of the employed measures of wanting, as reflected in the large observed standard deviations. The combination of a small sample size and substantial interindividual variability may therefore have reduced the likelihood of detecting statistically significant effects. In addition, the relatively homogeneous composition of the sample limits the generalizability of the findings to broader populations.

The validity of exerted effort as an objective measure of wanting may also be questioned. Several participants in the already small sample experienced difficulties using the hand dynamometer. Some reported that they were unable to make the "wanting bar" (the visual feedback indicating exerted effort) increase as intended, while others exerted little or no effort for low rewards, despite instructions to always apply some pressure. Although these issues could usually be resolved during testing, they may nevertheless have affected the reliability of exerted effort as an objective indicator of wanting, particularly given the limited sample size.

Another consideration concerns the standardization of participants' metabolic state. Hunger and satiety were not tightly controlled beyond general fasting requirements. Participants were instructed not to be hungry at the start of the procedure, but subjective hunger levels and prior food intake were not systematically assessed. Because both oxytocin responsiveness and reward sensitivity are influenced by physiological energy status, variability in hunger or satiety may have contributed to heterogeneity in drug responsiveness.

Taken together, these methodological considerations suggest that the present findings should be interpreted cautiously and within the specific experimental context in which they were obtained.

5.6 Future directions

Given that several factors within the present study may have contributed to the absence of significant effects of oxytocin and naltrexone on food-related incentive salience, future research may benefit from testing the proposed anorexigenic effects of both agents using modified experimental paradigms. To better capture mechanisms observed in clinical and naturalistic contexts, future studies could employ more ecologically valid settings that include self-regulated consummatory behavior as a direct outcome measure.

In addition, the use of highly palatable food rewards rich in sugar and fat and specifically designed to induce craving may help clarify the effects of naltrexone on food-related incentive salience in non-clinical samples. Such approaches may help determine whether reductions in hedonic hunger can also be observed in healthy populations under conditions characterized by stronger craving intensity.

Finally, future studies may benefit from employing food rewards that differ in macronutrient composition or energy density. This would allow researchers to examine whether the differentiation in wanting observed in the present study under controlled macronutrient conditions becomes more pronounced or mechanistically clearer when stimuli vary in nutritional properties such as fat or sucrose content, as opioid-related modulation of food reward would be expected to be more readily detectable under such conditions (Apfelbaum & Mandenoff, 1981; Head et al., 2021).

Conclusion

The present study examined the effects of oxytocin and naltrexone on homeostatic and hedonic facets of food-related incentive salience in healthy young women. Contrary to prior assumptions, neither single nor combined administration of the two drugs was associated with a reduction in wanting of food rewards. Furthermore, fMRI analyses did not reveal significant differences in blood-oxygen-level-dependent responses within reward- and satiety-related brain regions across experimental conditions.

Exploratory findings suggested that combined administration of oxytocin and naltrexone influenced the differentiation between the wanting of higher and lower reward foods, indicating the potential existence of additive effects on hedonic aspects of food-related

incentive salience. However, these effects were not consistently reflected across behavioral and neuroimaging measures and must therefore be interpreted cautiously.

Overall, the findings of the present study do not support the existence of robust anorexigenic effects of oxytocin or naltrexone on food-related incentive salience in healthy human populations under the applied experimental conditions. Future research using alternative paradigms, more ecologically valid settings, and more diverse samples will be necessary to clarify the mechanisms and boundary conditions of pharmacological influences on food-related incentive salience.

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Appendix

Appendix A: Statement on the Use of Artificial Intelligence

Artificial intelligence tools (OpenAI, ChatGPT) were used solely to correct spelling mistakes and to improve grammar and sentence clarity. AI was not used to generate ideas, develop hypotheses, or produce academic content in any form.

Appendix B: Exploratory SPM results tables from small-volume–corrected ROI analyses

Figure B1

SPM results table for the *oxytocin* > *placebo* contrast within the hypothalamus ROI (small-volume correction)

Statistics: *search volume: image mask: ..bels_(Hypothalamus)0.5mm.nii*

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.900	5	1.000	1.000	2	1.000	0.848	2.022	2.61	2.32	0.010	10	-8	-2
		1.000	1.000	740	1.000	0.885	2.022	2.51	2.25	0.012	-6	-18	-18
						0.934	2.022	2.35	2.13	0.017	-8	-16	-8
						0.938	2.022	2.34	2.11	0.017	14	-10	-8
						0.975	2.022	2.13	1.95	0.025	-14	-18	-8
						0.998	2.022	1.69	1.60	0.055	10	-26	-18
						0.998	2.022	1.68	1.59	0.056	-6	0	-6
						0.998	2.022	1.68	1.59	0.056	4	-8	-16
						0.999	2.022	1.66	1.58	0.058	-4	-8	-14
						0.999	2.022	1.58	1.51	0.066	-8	-4	-2
						1.000	2.022	1.51	1.45	0.074	-10	-12	-12
						1.000	2.022	1.51	1.44	0.074	6	-20	-18
						1.000	2.022	1.49	1.43	0.076	-14	-14	-12
						1.000	2.022	1.47	1.41	0.079	6	-12	-16
						1.000	2.093	1.28	1.26	0.104	4	-20	-14
						1.000	2.093	1.24	1.22	0.112	0	2	8
						1.000	2.093	1.20	1.19	0.118	2	-4	-10
		1.000	1.000	3	1.000	1.000	2.093	1.10	1.10	0.136	-10	-8	4
		1.000	1.000	1	1.000	1.000	2.185	-0.70	-0.07	0.529	10	-6	4
		1.000	1.000	1	1.000	1.000	2.185	-1.74	-0.29	0.612	-58	-20	32

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = -Inf, p = 0.632 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 390879749093385728.000
Expected number of clusters, <c> = 8.00
FWEp: 4.917, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 14.0]
FWHM = 9.2 9.1 8.4 mm mm mm; 4.6 4.5 4.2 {voxels}
Volume: 5976 = 747 voxels = 1.3 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 86.79 voxels)

Figure B2

SPM results table for the *placebo* > *oxytocin* contrast within the nucleus accumbens ROI (small-volume correction)

Statistics: ***search volume: image mask: .._res-epi_label-NAcc_mask.nii***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_E)	p_{uncorr}	
0.594	2	0.865	1.000	112	1.000	**0.771**	**1.454**	**1.49**	**1.43**	**0.077**	**4 6 -6**
						0.780	1.454	1.46	1.40	0.080	10 12 -12
		0.865	1.000	98	1.000	**0.943**	**1.454**	**0.32**	**0.48**	**0.314**	**-4 6 -4**
						0.944	1.454	0.29	0.47	0.321	-16 6 -10
						0.944	1.454	0.29	0.46	0.321	-8 14 -8
						0.944	1.454	0.29	0.46	0.322	-8 6 -14
						0.945	1.454	0.24	0.43	0.333	-8 10 -12
						0.945	1.454	0.20	0.40	0.343	-4 10 -8

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = -Inf, p = 0.632 (0.865)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 390879749093385728.000
Expected number of clusters, <c> = 2.00
FWEp: 3.989, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 14.0]
FWHM = 9.2 9.1 8.4 mm mm mm; 4.6 4.5 4.2 {voxels}
Volume: 1680 = 210 voxels = 0.8 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 86.79 voxels)

Figure B3

SPM results table for the *placebo* > *oxytocin* contrast within the ventral tegmental area ROI (small-volume correction)

Statistics: ***search volume: image mask: ..s-vta_avg-27sum-midbrain.nii***

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.000	**7**	**0.632**	**1.000**	**1682**	**1.000**	**0.945**	**5.673**	**2.49**	**2.23**	**0.013**	**-14**	**-8**	**-10**
						0.969	5.673	2.29	2.08	0.019	14	-24	-8
						0.972	5.673	2.25	2.05	0.020	-10	-6	-10
						0.973	5.673	2.25	2.05	0.020	10	-18	-10
						0.994	5.673	1.75	1.65	0.050	12	-16	-20
						0.994	5.673	1.72	1.62	0.053	6	-4	-4
						0.994	5.673	1.71	1.62	0.053	8	-16	-22
						0.994	5.673	1.69	1.60	0.055	4	-16	-6
						0.995	5.673	1.67	1.59	0.056	-12	-22	-2
						0.995	5.673	1.63	1.55	0.060	-12	-18	0
						0.996	5.673	1.56	1.49	0.068	0	-28	-2
						0.996	5.673	1.43	1.38	0.083	-14	-24	-14
						0.997	5.673	1.34	1.31	0.095	-18	-12	-8
						0.996	5.673	1.14	1.13	0.128	4	-22	-22
						0.996	5.673	1.11	1.11	0.134	-18	-20	-16
						0.996	5.673	1.09	1.10	0.136	-18	-6	-2
		0.632	**1.000**	**1**	**1.000**	**0.995**	**5.673**	**1.60**	**1.52**	**0.064**	**-6**	**-8**	**-22**
		0.632	**1.000**	**1**	**1.000**	**0.996**	**5.673**	**1.15**	**1.15**	**0.125**	**-12**	**-4**	**-14**
		0.632	**1.000**	**1**	**1.000**	**0.996**	**5.673**	**0.79**	**0.84**	**0.199**	**20**	**-26**	**-8**
		0.632	**1.000**	**1**	**1.000**	**0.993**	**5.673**	**0.39**	**0.53**	**0.297**	**-18**	**-30**	**-12**
		0.632	**1.000**	**1**	**1.000**	**0.961**	**5.673**	**-0.32**	**0.09**	**0.463**	**-18**	**-24**	**0**

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = -Inf, p = 0.632 (0.632)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 390879749093385728.000
Expected number of clusters, <c> = 1.00
FWEp: 5.656, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 14.0]
FWHM = 9.2 9.1 8.4 mm mm mm; 4.6 4.5 4.2 {voxels}
Volume: 13504 = 1688 voxels = 26.3 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 86.79 voxels)
Page 1

Figure B4

SPM results table for the *placebo* > *naltrexone* contrast within the nucleus accumbens ROI (small-volume correction)

Statistics: ***search volume: image mask: ..._res-epi_label-NAcc_mask.nii***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}	
0.594	**2**	**0.865**	**1.000**	**98**	**1.000**	**0.934**	**1.449**	**0.50**	**0.62**	**0.269**	**-10 10 -12**
						0.943	1.449	0.27	0.45	0.326	-8 6 -2
						0.945	1.449	0.15	0.37	0.357	-4 6 -4
						0.945	1.449	0.09	0.33	0.371	-8 14 -8
						0.953	1.000	-0.30	0.10	0.461	-4 10 -8
						0.952	1.000	-0.67	-0.06	0.525	-18 8 -10
		0.865	**1.000**	**112**	**1.000**	**0.944**	**1.449**	**0.16**	**0.37**	**0.355**	**10 12 -10**
						0.953	1.000	-0.36	0.07	0.472	4 6 -6

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = -Inf, p = 0.632 (0.865)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 405815806864395456.000
Expected number of clusters, <c> = 2.00
FWEp: 3.973, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 14.0]
FWHM = 9.2 9.2 8.5 mm mm mm; 4.6 4.6 4.2 {voxels}
Volume: 1680 = 210 voxels = 0.8 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 90.11 voxels)

Figure B5

SPM results table for the *placebo* > *naltrexone* contrast within the ventral pallidum ROI (small-volume correction)

Statistics: ***search volume: image mask: ..l_pallidum_bilateral_4mm.nii***

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_E)	p_{uncorr}			
0.594	**2**	**0.865**	**1.000**	**257**	**1.000**	**0.403**	**1.092**	**2.85**	**2.49**	**0.006**	**12**	**-2**	**-2**
						0.517	1.092	2.59	2.30	0.011	12	-8	0
		0.865	**1.000**	**257**	**1.000**	**0.834**	**1.794**	**1.79**	**1.68**	**0.046**	**-16**	**-8**	**0**
						0.974	1.924	0.74	0.81	0.209	-12	-10	-6
						0.977	1.924	0.62	0.71	0.239	-4	-4	0
						0.979	1.924	0.56	0.66	0.255	-4	-10	-4

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = -Inf, p = 0.632 (0.865)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 405815806864395456.000
Expected number of clusters, <c> = 2.00
FWEp: 4.481, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 14.0]
FWHM = 9.2 9.2 8.5 mm mm mm; 4.6 4.6 4.2 {voxels}
Volume: 4112 = 514 voxels = 3.0 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 90.11 voxels)

Figure B6

SPM results table for the *placebo* > *naltrexone* contrast within the amygdala ROI (small-volume correction)

Statistics: ***search volume: image mask: .\2B_Amygdala\r2Amy_bi.nii***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}	
0.594	**2**	**0.865**	**1.000**	**248**	**1.000**	**0.523**	**2.163**	**2.61**	**2.32**	**0.010**	**30 4 -18**
						0.810	2.163	1.94	1.80	0.036	28 -2 -20
						0.827	2.163	1.89	1.76	0.039	26 2 -28
						0.960	2.163	1.17	1.16	0.122	32 2 -30
		0.865	**1.000**	**220**	**1.000**	**0.954**	**2.163**	**1.24**	**1.22**	**0.110**	**-26 -2 -28**
						0.959	2.163	1.20	1.18	0.118	-22 -4 -26
						0.987	2.163	0.41	0.55	0.291	-30 -4 -14
						0.987	2.163	0.37	0.52	0.300	-28 -8 -12
						0.987	2.163	0.24	0.43	0.334	-26 0 -18
						0.986	2.163	0.18	0.39	0.349	-22 0 -12

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = -Inf, p = 0.632 (0.865)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 405815806864395392.000
Expected number of clusters, <c> = 2.00
FWEp: 4.464, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 14.0]
FWHM = 9.2 9.2 8.5 mm mm mm; 4.6 4.6 4.2 {voxels}
Volume: 3744 = 468 voxels = 2.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 90.11 voxels)

Figure B7

SPM results table for the *oxytocin + naltrexone > oxytocin* contrast within the hypothalamus ROI (small-volume correction)

Statistics: ***search volume: image mask: ..bels_(Hypothalamus)0.5mm.nii***

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.900	5	1.000	1.000	740	1.000	**0.148**	**0.681**	**4.15**	**3.30**	**0.000**	**-12**	**-18**	**-14**
						0.518	1.020	3.19	2.72	0.003	-6	2	-12
						0.525	1.020	3.18	2.71	0.003	10	-18	-8
						0.617	1.020	3.02	2.60	0.005	-8	-4	-12
						0.765	1.119	2.75	2.42	0.008	14	-22	-10
						0.831	1.119	2.61	2.32	0.010	6	4	-4
						0.842	1.119	2.59	2.30	0.011	-10	-8	-10
						0.962	1.264	2.18	1.99	0.023	4	-18	-8
						0.962	1.264	2.18	1.99	0.023	-16	-16	-4
						0.982	1.264	2.02	1.87	0.031	-22	0	-6
						0.983	1.264	2.02	1.87	0.031	24	0	-8
						0.991	1.264	1.90	1.77	0.038	8	2	-10
						0.991	1.264	1.90	1.77	0.039	2	6	-6
						0.992	1.264	1.88	1.76	0.040	8	-2	-12
						0.994	1.264	1.83	1.71	0.044	-24	-2	-10
						0.995	1.264	1.81	1.70	0.045	-4	-16	-10
		1.000	**1.000**	**1**	**1.000**	**0.936**	**1.264**	**2.31**	**2.09**	**0.018**	**-58**	**-20**	**32**
		1.000	**1.000**	**1**	**1.000**	**1.000**	**1.988**	**0.54**	**0.65**	**0.258**	**10**	**-6**	**4**
		1.000	**1.000**	**3**	**1.000**	**1.000**	**1.988**	**0.52**	**0.63**	**0.264**	**-10**	**-8**	**2**
		1.000	**1.000**	**2**	**1.000**	**1.000**	**2.122**	**-0.84**	**-0.12**	**0.548**	**10**	**-8**	**0**

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = -Inf, p = 0.632 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 43695516257990 4128.000
Expected number of clusters, <c> = 8.00
FWEp: 4.877, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 14.0]
FWHM = 9.5 9.4 8.7 mm mm mm; 4.7 4.7 4.3 {voxels}
Volume: 5976 = 747 voxels = 1.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 97.02 voxels)

Figure B8

SPM results table for the *oxytocin + naltrexone < naltrexone* contrast within the nucleus accumbens ROI (small-volume correction)

Statistics: *search volume: image mask: .._res-epi_label-NAcc_mask.nii*

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}	
0.594	**2**	**0.865**	**1.000**	**98**	**1.000**	**0.884**	**1.452**	**0.98**	**1.01**	**0.157**	**-14 6 -8**
						0.945	1.452	0.07	0.32	0.376	-14 14 -12
						0.948	1.000	-0.84	-0.12	0.547	-4 8 -4
						0.934	1.452	-1.29	-0.23	0.590	-8 10 -4
		0.865	**1.000**	**112**	**1.000**	**0.902**	**1.452**	**0.86**	**0.91**	**0.182**	**14 6 -10**
						0.922	1.452	0.68	0.76	0.223	6 14 -4
						0.928	1.452	0.61	0.70	0.242	10 10 -4
						0.951	1.000	-0.17	0.17	0.433	14 14 -10

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = -Inf, p = 0.632 (0.865)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 401378970363212928.000
Expected number of clusters, <c> = 2.00
FWEp: 3.978, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 14.0]
FWHM = 9.2 9.1 8.5 mm mm mm; 4.6 4.6 4.3 {voxels}
Volume: 1680 = 210 voxels = 0.8 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 89.12 voxels)

Figure B9

SPM results table for the *oxytocin + naltrexone* < *naltrexone* contrast within the ventral pallidum ROI (small-volume correction)

Statistics: ***search volume: image mask: ..l_pallidum_bilateral_4mm.nii***

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.594	**2**	**0.865**	**1.000**	**257**	**1.000**	**0.742**	**1.974**	**2.07**	**1.91**	**0.028**	**-16**	**-4**	**-8**
						0.978	1.974	0.59	0.68	0.247	-8	-12	-2
						0.980	1.974	-0.08	0.22	0.412	-12	-2	2
						0.978	1.974	-0.64	-0.05	0.520	-10	-6	4
		0.865	**1.000**	**257**	**1.000**	**0.902**	**1.974**	**1.51**	**1.44**	**0.074**	**8**	**-2**	**-6**
						0.981	1.974	0.15	0.36	0.358	6	2	0
						0.973	1.974	-0.88	-0.13	0.552	14	-4	2
						0.966	1.974	-1.12	-0.19	0.576	10	-8	0

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = -Inf, p = 0.632 (0.865)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 4013789703632128 28.000
Expected number of clusters, <c> = 2.00
FWEp: 4.486, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 14.0]
FWHM = 9.2 9.1 8.5 mm mm mm; 4.6 4.6 4.3 {voxels}
Volume: 4112 = 514 voxels = 3.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 89.12 voxels)

Declaration of Authorship

I hereby declare that this master's thesis is my own independent work. I have used no materials other than those cited herein, and all passages taken from other works have been properly acknowledged. This thesis has not been submitted previously in the same or similar form at any other institution.

Vienna, March 12, 2026

eh Oliver Erich Bichler