Dopaminergic and opioidergic regulation of implicit and explicit wanting and liking of social and nonsocial rewards

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Abstract

Rewards can be parsed into a motivational component ('wanting'), which relies mainly on the brain's dopaminergic system, and a hedonic component ('liking'), which relies on the opioidergic system. The observation of animal facial and behavioral reactions to rewards (e.g. pleasant tastes) has played a crucial role for our understanding of the neurochemical bases of reward processing. In adult humans, however, implicit facial reactions to reward anticipation and consumption are rarely reported, and the role that the dopaminergic and opioidergic systems play in human facial reactions to rewards remains largely unknown. It is also unclear, if human facial reactions to different types of rewards have the same neurochemical basis. To answer these questions, we conducted a study using a randomized, double-blind, between-subject design in which 131 volunteers (88 females) received orally either the D2/D3 receptor antagonist amisulpride (400 mg), the non-selective opioid receptor antagonist naltrexone (50 mg), or placebo. Explicit (ratings and physical effort) and implicit (facial EMG) reactions to matched primary social and nonsocial rewards were assessed on a trial-by-trail basis. Sweet milk with different concentrations of chocolate flavor served as nonsocial food reward. Gentle caresses to the forearm, delivered by the same-sex experimenter at different speeds, served as social reward. Results suggested 1) reduced wanting of rewards after administration of both dopamine and opioid receptor antagonists, compared to placebo, as indicated by less physical effort produced to obtain the announced reward and increased negative facial reactions during reward anticipation; 2) reduced liking of rewards only after administration of the opioid receptors antagonist, compared to placebo, as indicated by reduced positive and increased negative facial reactions during and following reward consumption. Most drug effects were either stronger or restricted to food trials, suggesting that wanting and liking of both social and nonsocial rewards may only partially share the same neurochemical brain substrates. The results are in line with the distinction of wanting and liking by current theories of reward, and

underline the importance of assessing implicit facial reactions when conducting research on reward processing in adult human participants.

Keywords

Reward; affective touch; food; dopamine; opioid; facial EMG; real effort; wanting; liking

Introduction

Rewards are salient stimuli, objects, events, and situations that induce approach and consummatory behavior by their intrinsic relevance for survival or because experience has taught us that they are pleasurable [1]. Rewards can be parsed, at the psychological, neurophysiological, and neurochemical level, into 'wanting' (the motivation to mobilize effort to obtain a reward), 'liking' (the hedonic response evoked by its consumption), and learning [2–4]. This conceptual division is paralleled in cognitive theories of economic decision making [5,see also 6] that similarly distinguish between 'decision utility' (how much the value attached to an outcome determines its choice or pursuit), and 'experienced utility' (referring to the subjective hedonic experience generated by an outcome). Today, our understanding of wanting and liking rests on 30 years of animal research, and on preliminary confirmatory findings in humans, and has been shown to have important implications for affective and addictive disorders, including substance abuse and schizophrenia [7].

Wanting is mainly linked to the mesolimbic dopaminergic system, and is dissociable from liking, as suggested for example by the "taste reactivity test", a method to assess eating-related pleasure by observing facial and bodily reactions of animals and human infants to palatable and aversive tastes [8]. For instance, neither pharmacological disruption, nor extensive lesion of dopaminergic neurons affects facial liking reactions to sweet tastes in rats [9,10], but increased mesolimbic dopamine release induced by electric stimulation of the hypothalamus results in greater wanting to eat without modulating liking [11]. Evidence that the dopaminergic system underlies wanting also exists in humans. For example, stimulation of D2/D3 dopamine receptors through dopamine agonists can induce compulsive gambling, shopping, hypersexuality, and other compulsive activities in some patients with Parkinson's disease [12]. These addictive behaviors, which correspond to strong urge-like wanting without changes in liking, are accompanied by altered activations in the ventral striatum and prefrontal cortex, which however normalize when patients are off dopaminergic medication

[13]. Furthermore, Parkinson's disease patients can become sensitized to dopaminergic drugs, which provoke hyper reactivity of the mesolimbic dopaminergic system. These patients use their medication compulsively, and the induced dopamine release in the ventral striatum correlates with drug wanting but not liking [14]. A handful of recent studies in healthy volunteers have also suggested that dopamine is related to motivational but not hedonic aspects. For example, dopamine D2/D3 receptor blockade with amisulpride disrupted the motivation to gain immediate rewards in both a pavlovian-instrumental-transfer task and a delay discounting task [15], and reduces the rewarding value of prosocial decisions in women [16]. Moreover, intake of d-amphetamines results in increased dopamine release in the ventral striatum, as shown with positron emission tomography (PET), and these changes correlate with participants' wanting [17].

Liking, which was long believed to rely on dopamine neurotransmission [18], may instead by mediated by the opioidergic system. The evidence in favor of this assumption stems again mostly from animal research, which has identified small parts of the brain called "hedonic hotspots", including the nucleus accumbens (NAc) shell and part of the limbic system that are responsive to opioidergic stimulation, and are able to amplify hedonic reactions to sensory pleasure [3]. However, the opioidergic system partly also affects wanting by modulating the impacts of dopamine in the NAc [19]. Indeed, injections of μ and δ opioid receptor agonists have been shown to increase food approach and feeding behavior, especially for palatable and high-energy foods [20], which shows that opioids primarily affect wanting through liking. Similar evidence in humans suggest that μ opioid receptor agonists increase the subjective pleasantness of the most palatable food option available [21], and both subjective feelings of wanting and liking of the most attractive opposite sex faces [22]. In contrast, the non-selective opioid receptor antagonist naloxone decreases subjective pleasure (liking) associated with viewing erotic pictures and reduces the activation of reward related brain regions such as the ventral striatum [23]. In summary, wanting relies mostly on the

dopaminergic system and – through changes in liking – also on the opioidergic system. Liking, on the other hand, relies mostly on the opioidergic but not the dopaminergic system.

In spite of the progress made with past research, a clear understanding of the neurochemical regulation of wanting and liking in healthy humans, especially across multiple reward types, is still lacking. A major challenge towards attaining that goal may be the development of a paradigm that resembles those used in animal research, and thus an operationalization of the wanting and liking concepts that allows trans-species comparison. Indeed, while the decision utility (wanting) of a reward is easily inferred from observed choices, such as purchasing a good, the concomitant experience utility (liking) is more challenging to measure objectively. In human newborns, juvenile monkeys, and adult rats the consumption of food rewards elicits powerful and distinctive facial reactions [8,24,25]. The taste reactivity test [8] has indeed become the gold standard to assess hedonic pleasure in animal models. Importantly, following Pavlovian conditioning, animals also show facial reactions to cues (thus before reward delivery) that they have learned to associate with the delivery of the unconditioned taste stimuli [26]. However, facial reactions to pleasant tastes and other types of reward are more subtle in adult humans, and have only started to be investigated using facial electromyography (EMG) [27–31]. Recently, we have shown [27] that in healthy human adults the anticipation and consumption of food rewards results in the relaxation of the main frowning muscle corrugator supercilii (CS), and that the experience of social touch rewards elicits activation of the main smiling muscle, the zygomaticus major (ZM). The latter result emerged from explorative analyses, but others have also reported ZM contraction and CS relaxation in response to pleasant social touch [28–30]. Human adults thus relax the CS and activate the ZM during both the anticipation and the consumption of rewards, although differences between types of rewards may also exist. However, it remains unknown how these facial reactions rely on the dopaminergic and opioidergic systems, and whether they can be modulated by corresponding pharmacological manipulations.

To fill this gap of knowledge, we pharmacologically manipulated the dopaminergic and opioidergic systems in human adults and measured both explicit (ratings, physical effort) and implicit (facial EMG) reactions to social and food rewards. This allowed us to address two fundamental unresolved research questions: 1) to what extent motivational and hedonic implicit and explicit responses rely on the dopaminergic and opioidergic systems in humans, and 2) whether the neurochemical basis of human reward processing differs for social (touch) and nonsocial (food) rewards. To address these questions and to overcome some of the limitations of past research [32], we used a recently developed experimental paradigm [27], that includes – on a trial-by-trial basis and in the same participants – anticipation and consumption of social and nonsocial rewards (although facial reactions occurring during the anticipation of learned rewards may reflect anticipatory pleasure, we here refer to them as wanting, as they can nevertheless differ from those related to liking of a consumed reward). Importantly, the paradigm allows for the comparison of social and nonsocial rewards that are matched for subjective wanting and liking and share some relevant fundamental properties, such as being considered primary, i.e. for which a biological preparedness can be expected. Implicit facial EMG reactions of the ZM and CS muscles during both the anticipation and the consumption of these rewards, and explicit subjective ratings and physical effort were recorded. Sweet milk with different concentrations of chocolate flavor served as food reward. Gentle caresses to the forearm at different speeds, resulting in different levels of pleasantness [33–35], served as social rewards. In each trial of the experiment (Fig. 1), wanting of an announced reward was measured through subjective ratings, facial reactions, and exerted physical effort (squeezing of an individually thresholded hand-dynamometer) – the amount of physical effort linearly predicted the probability to receive the announced reward or, alternatively, the least-liked reward. Participants obtained a reward in every trial (either the announced high or low reward, or the verylow reward following insufficient effort), and its

liking was measured with subjective ratings and facial reactions during and immediately after its delivery.

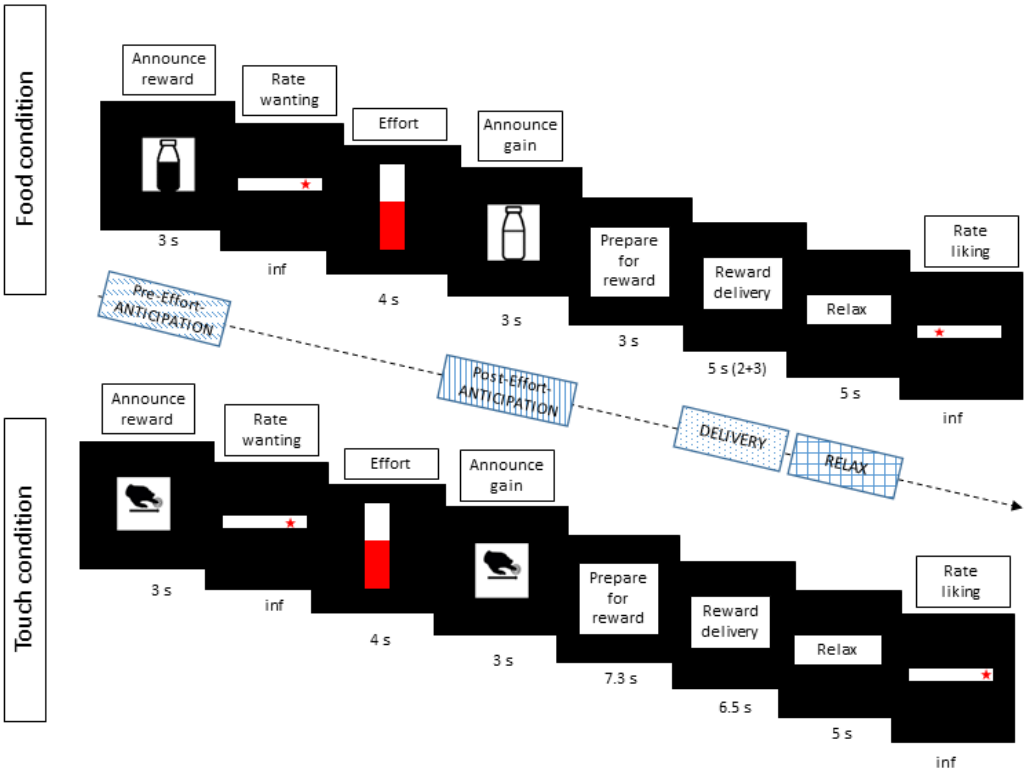

Fig. 1: Main elements in each trial for the Food and Touch conditions. Before the main task, participants ranked three rewards per condition by liking. In the main task (here depicted), one of the two most liked rewards (high and low) was announced at the beginning of each trial. The probability of obtaining the announced reward was determined by participants' hand-squeezing effort, and indicated in real-time. The gained reward (which was either the one announced at the beginning of the trial, or the least-liked verylow reward if squeezing was not sufficient) was then announced and delivered. To assess reward anticipation, EMG data was analyzed during the Pre-Effort anticipation period (3 sec) at the beginning of the trial, when a possible reward was announced, as well as during the Post-Effort anticipation period (3 sec announcement) preceding reward delivery. To investigate reward consumption, EMG data was analyzed during reward Delivery (5 sec in the Food, and 6.5 sec in the Touch condition), and in the immediately following Relax phase (5 sec). "Inf" (under ratings) symbolizes that ratings slides stayed on screen indefinitely, or until participants' button press. For a complete representation of all trial elements see Fig. S1 in the Supporting Information.

The role of the dopaminergic and opioidergic systems was investigated using oral administration of the highly selective D2/D3 receptor antagonist amisulpride (400 mg), the non-selective opioid receptor antagonist naltrexone (50 mg), or placebo three hours before the task, in a randomized, double-blind, between-subject design in 131 healthy volunteers. The

sample size was chosen based on previous work employing the same compounds and doses [15].

We hypothesized that 1) greater wanting and liking would lead to greater effort, ZM activation, and CS deactivation; 2) administration of the D2/D3 receptor antagonist amisulpride would reduce wanting; and 3) administration of the non-selective opioid antagonist naltrexone would reduce both wanting and liking. Finally, based on evidence from neuroimaging studies that supports the 'common currency hypothesis' of reward processing [3,36], we expected 4) the same pattern of results for food and touch rewards.

Results

Matching of drug groups

Given that the type of reward received in each trial depended on both the announcement cue at the beginning (high or low) and the force exerted to obtain it (verylow rewards were only obtained following insufficient effort), we tested for differences in the number of reward types across groups. The number of trials with high, low, or verylow rewards did not differ across groups, as shown by a linear mixed effects model (LMM) with number of trials as dependent variable, the fixed effects Condition (social, nonsocial), Drug (amisulpride, naltrexone, placebo), and Reward Type (high, low, verylow), and by-subject random intercepts for Condition, Reward Type, and their interaction. Only a significant main effect of Reward Type was found ($F(2, 763) = 27.84$, $p < .001$), due to a greater number of high ($M = 16.53$, $SD = 2.87$) than low ($M = 14.93$, $SD = 3.46$) and verylow ($M = 8.67$, $SD = 4.93$) trials across all three groups.

Moreover, groups did not differ in their maximum voluntary contraction (MVC) of the hand dynamometer, which was measured right before the main task ($\beta = 1.6$, $SE = 8.68$, $t = 0.19$, $p = 0.85$), nor in their positive and negative mood at time of pill intake or three hours later (all $\beta < 0.6$, all $t < 0.8$, all $p > 0.4$).

Explicit measures: ratings of wanting, effort, and ratings of liking

Subjective ratings of wanting and liking, as well as effort were each analyzed in separate LMMs with Condition (social, nonsocial), Drug (amisulpride, naltrexone, placebo), and Reward Type (high, low announced at the beginning of each trial for wanting and effort; high, low, verylow obtained after the effort phase for liking) as fixed effects, and as random effects intercepts for subjects and by-subject random slopes for the effects of Condition, Reward Type, and their interaction. Only significant main and interaction effects for the factor Drug are reported, as they are most relevant to the study. Please see the Supporting Information for exhaustive documentation of statistical results (see also Fig. S2).

No main or interaction effects with the factor Drug were found for ratings of wanting. Behavioral analyses on effort resulted in a significant Condition X Drug interaction (Fig. 2A, $F(1, 128.31) = 4.54$, $p = .01$) reflecting lower effort in the food condition in the amisulpride ($M = 74.98$, $SD = 26.57$) and naltrexone ($M = 73.51$, $SD = 24.43$) groups compared to the placebo group ($M = 80.20$, $SD = 22.41$), but similar effort across drug groups in the social condition (amisulpride: $M = 78.34$, $SD = 25.14$; naltrexone: $M = 73.78$, $SD = 23.15$; placebo: $M = 76.11$, $SD = 23.51$). A marginally significant Reward Type X Drug interaction (Fig.2B) was also found ($F(1, 128.50) = 2.97$, $p = .05$), which was related to reduced effort to low rewards in the amisulpride ($M = 71.67$, $SD = 27.60$) and naltrexone ($M = 67.90$, $SD = 24.45$) groups compared to the placebo group ($M = 75.65$, $SD = 23.60$), but no such difference in the high rewards (amisulpride: $M = 81.60$, $SD = 23.09$; naltrexone: $M = 79.29$, $SD = 21.70$; placebo: $M = 80.63$, $SD = 22.23$). All other effects were not significant (all $F < 0.9$, all $p > .4$).

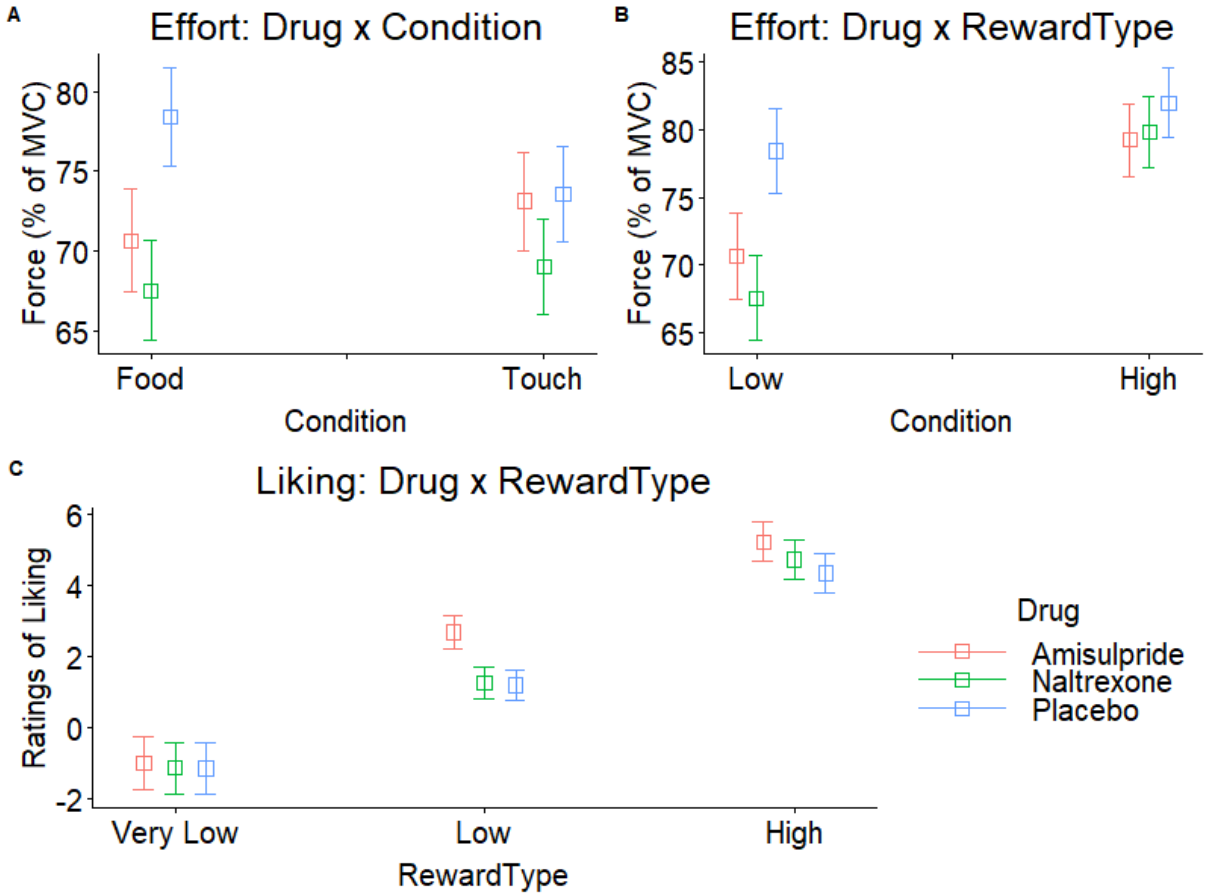

Fig. 2: Marginal means (and 95% CIs) for behavioral analyses. Physical effort was reduced in the amisulpride and naltrexone groups compared to placebo in (A) the food condition, and (B) for low rewards. (C) Liking of low rewards was greater in the amisulpride compared to the naltrexone and placebo groups.

The same LMM on the ratings of liking (Fig. 2B) resulted in a significant Drug X Reward Type interaction ($F(4, 259.62) = 11.07$, $p < .001$), reflecting greater liking of low rewards in the amisulpride group ($M = 2.57$, $SD = 3.78$), compared to the naltrexone group ($M = 1.33$, $SD = 4.35$), and the placebo group ($M = 1.53$, $SD = 4.18$).

In summary, the amisulpride and naltrexone groups showed reduced effort to obtain food rewards, and to obtain low rewards of both conditions. The amisulpride group also showed greater liking of low rewards compared to both the naltrexone and placebo groups.

Implicit measures: facial EMG

Facial EMG analyses were carried out separately for the CS and ZM muscles in four periods of interest (see Fig. 1): “Pre-effort anticipation” during reward announcement at the

beginning of each trial, "Post-effort anticipation" during the announcement of the gained reward, "Delivery", and "Relax". The EMG of Pre- and Post-Effort anticipation periods was analyzed in relation to ratings of wanting and to effort, as these measures were taken close in time. For the same reason, EMG of the Delivery and Relax periods was analyzed in relation to ratings of liking.

We first investigated if facial EMG reflected wanting and/or liking independently of Drug, by regressing the EMG of each muscle onto the factors Condition (food, touch) and either Wanting, Liking, or Effort (capitalized to indicate that they are factors in statistical models). Several main or interaction effects were found, showing that facial EMG was sensitive to changes in reward value, and that it was partly related to participants' explicit measures of wanting and liking (Figure 3). Activation of the CS muscle was inversely related to Wanting ($F(1, 138) = 8.00$, $p = .005$) and to Effort ($F(1, 150.13) = 10.33$, $p = .002$) in the Pre-Effort anticipation period, and to Liking in the Delivery ($F(1, 104.2) = 4.45$, $p = .04$) and Relax period ($F(1, 128.95) = 13.67$, $p < .001$; but more so in the food condition, as reflected by a Liking X Condition interaction: $F(1, 151.91) = 4.03$, $p = .05$). In contrast, activation of the ZM muscle was positively related to Wanting in the Pre-Effort anticipation period (but only for food, as shown by a Wanting X Condition interaction: $F(1, 7232.9) = 11.73$, $p < .001$), and in the Post-Effort anticipation period ($F(1, 131.44) = 6.39$, $p = .013$).

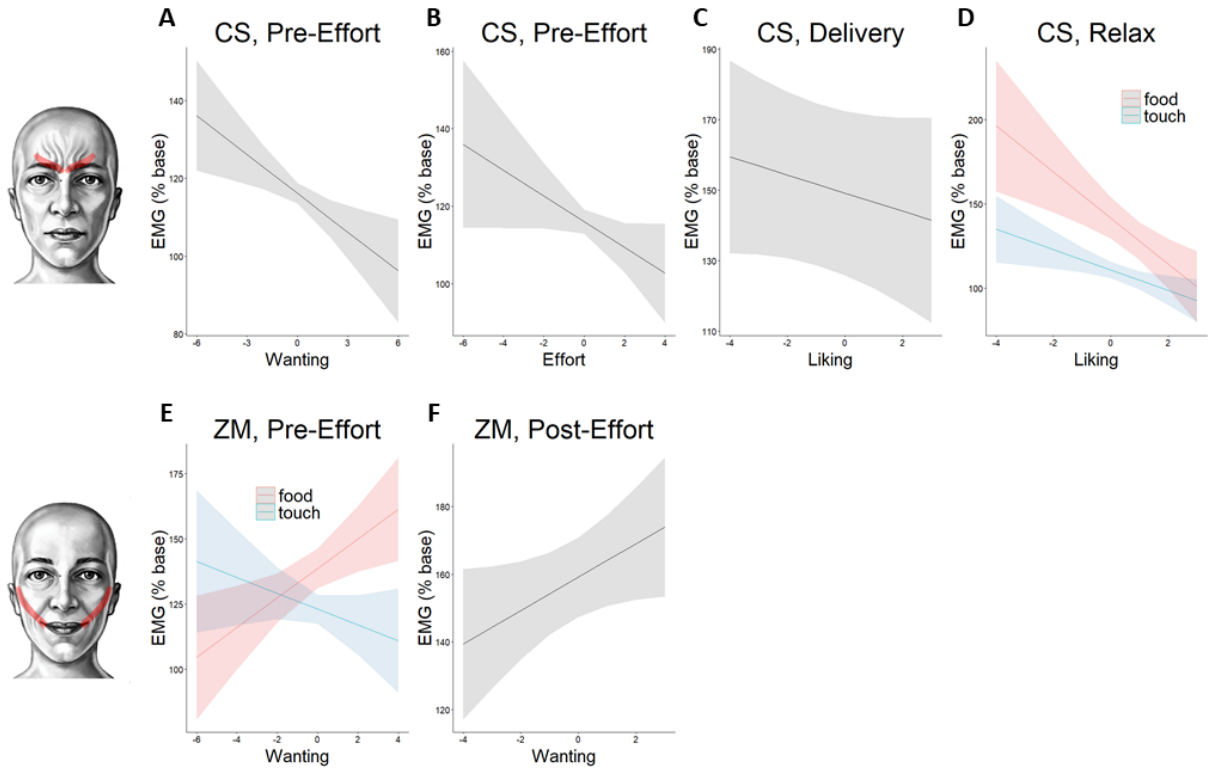

Fig. 3: Results (fit lines and and 95% CIs) of analyses investigating the sensitivity of facial EMG to wanting and liking of the administered rewards.The CS muscle relaxed with greater (A) wanting and (B) effort (Pre-Effort anticipation period), and with (C, D) greater liking (Delivery and Relax periods). The ZM muscle (E, F) activated with greater wanting in the Pre- and Post-Effort anticipation periods. Two interactions with Condition also occurred, reflecting greater effects in the nonsocial (food) than social (touch) condition.

Next, LMM analyses were carried out to investigate group differences in the facial EMG. These included the factors Condition (food, touch), Drug (amisulpride, naltrexone, placebo), and either Wanting or Effort for the Pre- and Post-Effort anticipation periods, or Liking for the Delivery and Relax periods. Random intercepts for subjects and by-subject random slopes for Condition and Wanting (or Effort/Liking), and their interaction, were included unless indicated otherwise. Only main and interaction effects involving the factor Drug are reported, as they are the most relevant to the study's hypotheses. Please see the Supporting Information for complete statistical results.

Pre-Effort anticipation

For the CS muscle by Wanting, a significant Drug X Condition interaction ($F(2, 129.42) = 4.73$, $p = .01$) reflected (Fig. 4) greater CS activation to food than touch in the amisulpride group ($p = .004$; Food: $M = 119.12$, $SD = 134.43$; Touch: $M = 109.46$, $SD = 76.09$) and naltrexone group ($p < .001$; Food: $M = 120.00$, $SD = 128.19$; Touch: $M = 109.66$, $SD = 89.46$), while the placebo group had similar activations across both conditions ($p = .68$; Food: $M = 110.30$, $SD = 65.72$; Touch: $M = 111.44$, $SD = 78.17$). All other effects were not significant (all $F < 2.2$, all $p > .1$).

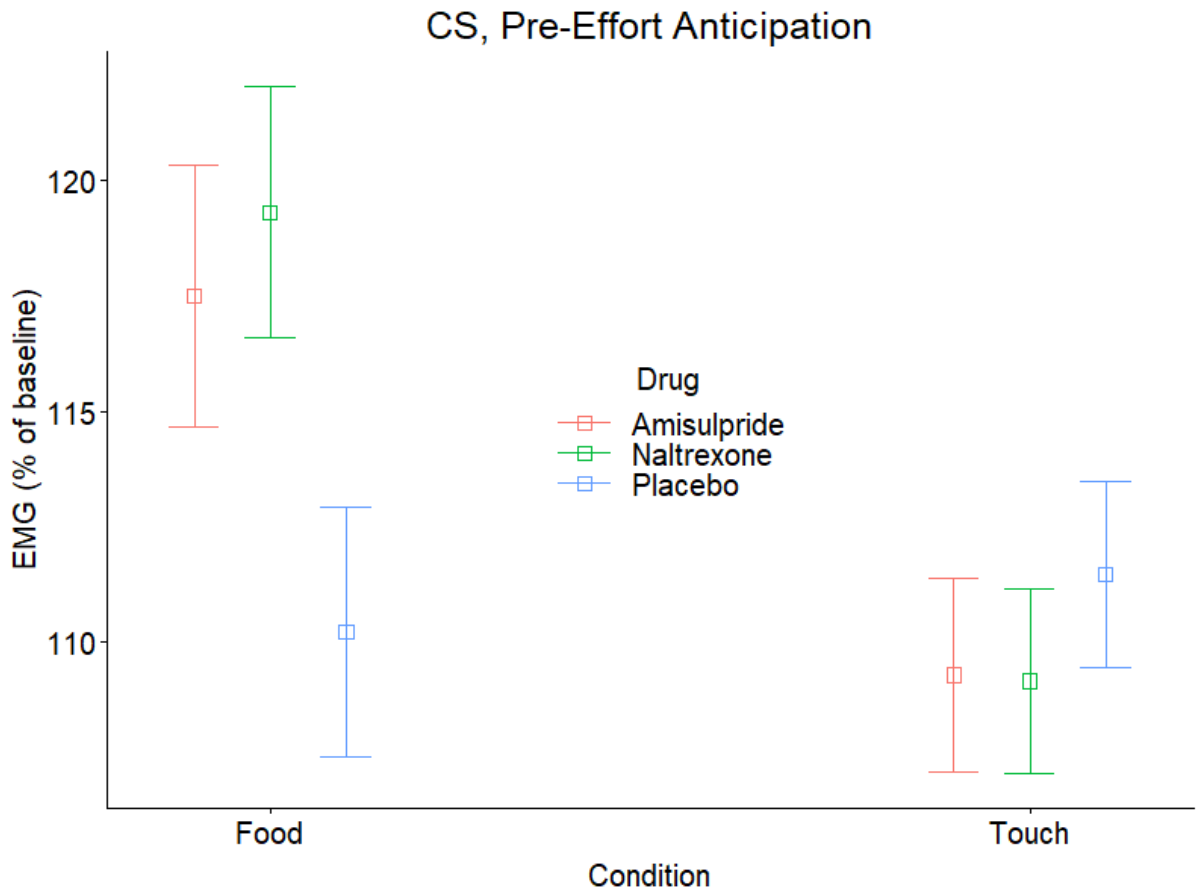

Fig. 4: Marginal means (and 95% CIs) of the EMG of the CS muscle in the Pre-Effort anticipation window. A significant Condition x Drug interaction was found for the model including the predictor Wanting (shown here), and similarly for the model including the predictor Effort.

Similarly, a significant Drug X Condition interaction was found in the analysis of the CS muscle by Effort ($F(2, 135.26) = 5.09$, $p = .007$), reflecting greater CS activation to food

than touch in the amisulpride ($p = .002$) and naltrexone group ($p < .001$), while the placebo group had similar activations across both conditions ($p = .71$). For the ZM muscle by Wanting and by Effort, no significant main effects or interactions involving the factor Drug were found (all $F < 2$, all $p > .1$).

In summary, activation of the CS in the Pre-Effort anticipation period was increased for food compared to touch stimuli in both active drug groups, but not in the placebo group.

Post-Effort anticipation

No significant main or interaction effects involving the factor Drug were found for the CS nor the ZM muscle (all $F < 1.9$, all $p > .15$).

Reward Delivery

No significant main or interaction effects involving the factor Drug were found for the CS by Liking (all $F < 7$, all $p > .5$). For the ZM, a significant Liking X Drug interaction was found ($F(2, 125.21) = 3.29$, $p = .04$). In the placebo group (Fig. 5), the slope for ZM activation with greater liking was significantly steeper than for the naltrexone group ($p = .03$). Comparisons of placebo with amisulpride and amisulpride with naltrexone were not significant (all $p > .3$).

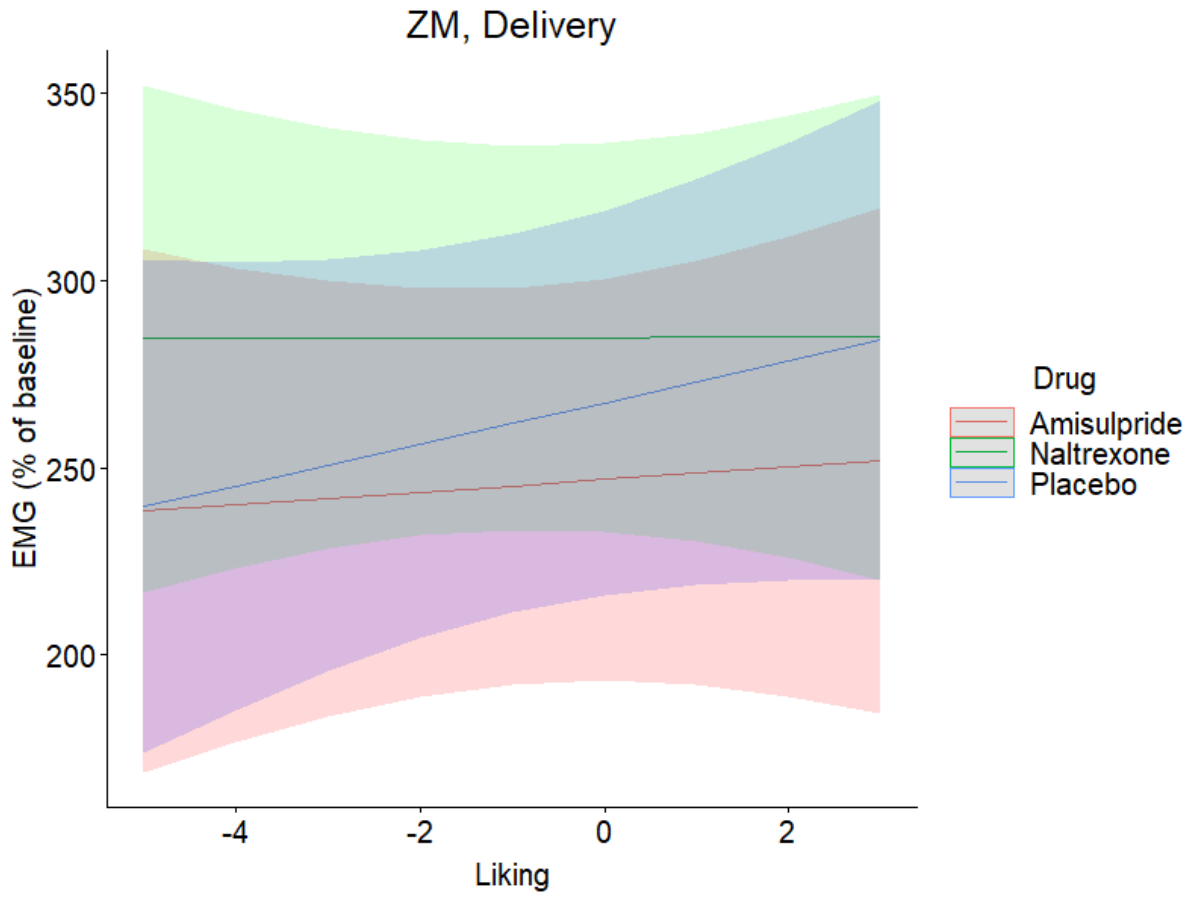

Fig. 5: Model fit (and 95% CIs) of the ZM in the Delivery window. A significant Liking x Drug interaction reflected ZM activation for greater Liking in the placebo group, but not in the naltrexone group.

Relax phase

In the analysis of CS muscle activation by Liking (the random slope for Condition was removed to allow model convergence), a significant Drug X Condition interaction was found ($F(2, 22902.1) = 3.80$, $p = .02$). In the food condition, CS activation was greater in the naltrexone group ($M = 161.22$, $SD = 479.78$) than in the amisulpride ($M = 132.93$, $SD = 191.94$; $p = .04$) and placebo ($M = 134.36$, $SD = 138.97$; $p = .05$) groups (Fig. 6). CS activations did not differ between groups in the touch condition (all $p > .6$).

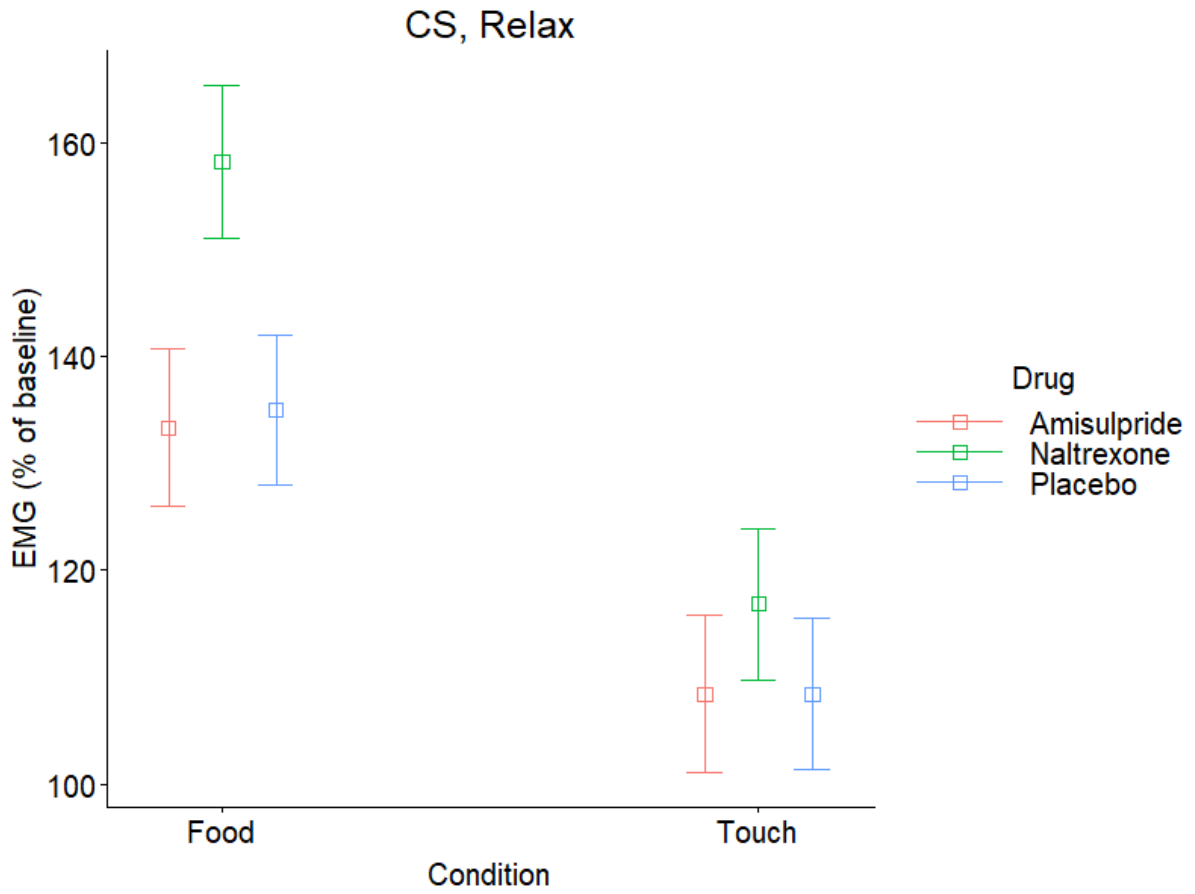

Fig. 6: Marginal means (and 95% CIs) of the CS in the Relax period. A significant Condition x Drug interaction reflected greater CS activation for Food in the naltrexone group.

No significant main or interaction effects involving the factor Drug were found for the ZM muscle (all $F < .9$, all $p > .3$).

Discussion

In this study, we used a recently developed experimental paradigm [27] that on a trial-by-trial basis assesses both explicit (ratings and effort) and implicit (facial EMG) anticipation (wanting) and consumption (liking) of social and nonsocial rewards in human participants. This paradigm, in combination with a dopaminergic or opioidergic drug challenge, allowed us to address two fundamental and as of yet unresolved research questions: 1) to which extent motivational and hedonic responses in adult humans rely on the same or different neurochemical systems, and 2) whether the neurochemical basis of human reward processing differs for social and nonsocial rewards. Analyses of the explicit measures revealed (Fig. 2)

that participants who had taken either the D2/D3 dopamine receptor antagonist amisulpride, or the non-selective opioid receptor antagonist naltrexone, produced less effort compared to placebo to 1) obtain food rewards, and 2) to obtain low rewards of both conditions. These findings are in line with the hypothesis that both the dopaminergic and the opioidergic systems underlie wanting [19]. The fact that the effect was observed for the second-preferred (low) reward, but not for the most preferred (high) reward, rules out the possibility of a generic motor impairment (e.g. induced by dopaminergic blockage). Instead, the results speak for a genuine alteration of the incentive salience of the low reward in both the amisulpride and the naltrexone groups.

Ratings of liking for low rewards was lower in the naltrexone than in the amisulpride group. Together with the finding of reduced effort in the amisulpride compared to the placebo group, this seems to corroborate the hypothesis that the dopaminergic system underlies the motivational but not the hedonic component of rewards, and that the opioidergic system underlies both. However, the fact that liking of low rewards was also lower in the placebo compared to the amisulpride group, suggests that these findings should be interpreted with caution.

Initial analyses of the EMG, without the factor Drug, confirmed the pattern expected based on prior work [27,28,30,37,38], of less frowning and more smiling during anticipation and consumption of wanted and liked rewards (Fig. 3). As we have recently reported using the same paradigm [27], most effects were in the CS muscle, which relaxed for greater wanting and effort in the Pre-Effort anticipation period, and for greater liking in the Delivery and Relax periods (the latter effect was stronger in the food condition). The ZM muscle showed the opposite pattern of activation for greater wanting in the Pre and Post-Effort anticipation periods (the first effect was only present in the food condition). The sensitivity of facial EMG for capturing wanting and liking was thus confirmed, although effects were, as in previous work [27], more prominent for the CS than the ZM muscle.

Next, we tested if activation patterns of the two muscles were modulated by the Drug. Both amisulpride and naltrexone resulted in greater CS activation during the Pre-Effort anticipation of food (Fig. 4). Because frowning typically reflects a more negative (or less positive) reactions [39,40], the fact that dopamine and opioid antagonists lead to greater frowning during reward anticipation might be interpreted as a reflection of less wanting in these groups of participants. During reward Delivery and Relax, only effects of naltrexone on facial reactions were observed. In particular, an expected increased ZM activation for greater liking was found in the placebo during Delivery, but not in the other groups of participants, and the slope of this effect was significantly steeper in the placebo than in the naltrexone group (Fig. 5). The fact that administration of the opioid antagonist naltrexone impaired smiling during the delivery of liked rewards supports the hypothesis that liking (experienced pleasure) requires a functioning opioidergic system. Similarly, in the Relax period just after reward delivery, greater CS activation for food rewards was found in the naltrexone group compared to both the amisulpride and placebo groups (Fig. 6). This result suggests again less hedonic pleasure (as indicated by increased frowning) immediately after the consumption of food rewards, when the opioidergic system is impaired.

Taken together, facial EMG data showed a differential action of dopaminergic and opioidergic drug challenges during the anticipation and consumption of rewards. In line with the explicit measures (ratings of wanting, ratings of liking and physical effort), the implicit measure of EMG indicates an effect of both amisulpride and naltrexone during the anticipation of rewards, but only of naltrexone during or immediately after reward consumption. This pattern of results corroborates, and extends to adult humans, previous animal evidence about the role of the dopaminergic system for the motivational but not hedonic component of reward processing, and of the opioidergic system for both wanting and liking.

There is currently a debate in the field [36], that pits the hypothesis of an identical neural substrate for the processing of different types of rewards (the 'common currency hypothesis') against the hypothesis that representations coding for different rewards occur in distinct neural structures, albeit on a common scale [41]. Social rewards in particular may constitute a separate class of stimuli, with a dedicated neural circuitry [42], which can be specifically impaired, for example in people with autism spectrum disorders [43].

Therefore, both social (touch) and nonsocial (food) rewards were administered in this experiment. Most drug effects were either stronger or restricted to food trials, e.g. in the Pre-Effort anticipation and Relax phase (but not in the Delivery period). A possible explanation for the less pronounced drug effects in the touch condition is that responses to social rewards, including touch, might also depend on oxytocin and serotonin, in addition to dopamine and opioids [44,45]. Indeed, amisulpride not only blocks dopamine D2/D3 receptors, but can also have off-target effects on 5-HT7 receptors. However, the serotonin system may be more relevant for the processing of punishments, than of rewards [46], making it rather unlikely that the observed effects of amisulpride on social rewards (or lack thereof) were mediated by the serotonin system. Future studies may however want to investigate the role of further neurochemical systems in the processing of social vs. nonsocial rewards.

Conclusion

We found pharmacological evidence in healthy human volunteers, across both explicit and implicit measures, for the hypothesis that wanting of rewards relies on the dopaminergic system, and liking of rewards relies on both the dopaminergic and opioidergic systems. This is, to the best of our knowledge, the first demonstration of this kind in adult humans, using a real-effort task in which physical rewards are anticipated and consumed in every trial, and in which frowning and smiling muscles are monitored with facial EMG. Most drug effects were either stronger or restricted to food trials, suggesting that wanting and liking of both social and nonsocial rewards may not rely on exactly the same neurochemical brain substrates.

Ultimately, a clear answer to the question if different rewards are processed in the same or different brain areas likely requires the use of brain imaging, or other more direct measures of brain activity, in addition to pharmacological challenges tailored to investigate the role of different neurochemical systems in the processing of social vs. nonsocial rewards.

Materials and Methods

Subjects

Based on previous work that had used the same compounds and doses [15], we aimed at collecting data from roughly 40 participants per group. The final participants sample included 131 volunteers (88 females) aged 18–35 years (M = 23.3; SD = 3.5). Participants who had taken amisulpride had blood concentrations of the drug (measured five hours after intake) that were in or above the therapeutic range (blood samples not available for six people). Specifically, the minimum was 212 ng/ml, and 19 participants were above 604 ng/ml. All participants reported being right-handed, to smoke less than five cigarettes daily, to have no history of current or former drug abuse, to like milk and chocolate, not to suffer from diabetes, lactose intolerance, lesions or skin disease on the left forearm, and to be free of psychiatric or neurological disorders. Participants' average Body Mass Index (BMI) was 22.6, (SD = 2.5, range 17.7 – 29.3). To reduce the chances that social touch would be perceived as a sexual reward, the social touch stimulation was always carried out by a same-sex experimenter (see Procedure), and only participants who reported to be heterosexual were included. The study was approved by the Ethical Committee of the Medical University of Vienna (EK N. 1393/2017) and performed in line with the Declaration of Helsinki [47]. Participants signed informed consent and received a monetary compensation of 90€.

Stimuli

Three stimuli with identical fat and sugar content (1.5 g fat, 10 g of sugar per 100 g) were used as rewards in the Nonsocial condition: milk, chocolate milk, and a 4:1 mix of milk and chocolate milk. Tap water served for rinsing at the end of each trial. The initial stimulus

temperature of these liquids was kept constant (~4° C) across participants. Stimulus delivery was accomplished through computer-controlled pumps (PHD Ultra pumps, Harvard Apparatus) attached to plastic tubes (internal ø 1,6 mm; external ø 3,2 mm; Tygon tubing, U.S. Plastic Corp.), which ended jointly on an adjustable arm positioned about two centimeters in front of the participant's mouth. On each trial, two ml of liquid were administered during two seconds. Overall, including stimulus pretesting (see Procedure), participants consumed 196 ml of liquids, composed of 98 ml of water, and 98 ml of sweet milk with different concentrations of chocolate aroma (depending on effort, see below).

Social rewards consisted of gentle caresses over a previously-marked nine-cm area of the participant's forearm (measurement started from the wrist towards the elbow). Three different caressing frequencies, chosen based on pilot testing, were applied during six seconds by a same-sex experimenter: six cm/s, 21 cm/s and 27 cm/s. To facilitate stroking, the stimulating experimenter received extensive training and in each trial heard the stimulation rhythms through headphones.

EMG

After cleansing of the corresponding face areas with alcohol, water, and an abrasive paste, Ag/AgCl electrodes were attached bipolarly according to guidelines on the left corrugator supercilii (CS) and the zygomaticus major (ZM) muscles [48]. A ground electrode was attached to the participants' forehead, and a reference electrode on the left mastoid. Results are here reported for the CS and ZM muscles. EMG data was sampled at 1200 Hz with impedances below 20kOHM using a g.USBamp amplifier (g.tec Medical Engineering GmbH) and the Matlab software (MathWorks, Inc.).

Procedure

A monocentric, randomized, double-blind, placebo-controlled, three-armed study design was used. The study took place in the Department of Psychiatry and Psychotherapy at the Medical University of Vienna. Participants visited the laboratory for a first visit (T0) in

which they received a health screening, followed by a second visit (T1) that included oral drug intake and the experiment described here. Pharmacological dosage, and length of waiting time after drug intake (three hours) were modeled on previous work [15].

Participants came to T1 with an empty stomach (no food in the preceding six hours), filled out the PANAS questionnaire, tested negative on a urine drug screen sensitive to opiates, amphetamine, methamphetamine, cocaine (among other things), and then received from the doctor a capsule filled with either 400 mg of amisulpride (Solian®), 50 mg of naltrexone (Dependex®), or 650 mg of mannitol (sugar). All capsules looked identical from the outside, and neither participants nor the experimenters were informed of their content. Drug intake was followed by a waiting period, EMG preparation, and task instructions.

The experiment comprised two tasks following procedures described elsewhere [27]. The main task started three hours after pill intake. Participants were seated at a table and comfortably rested their left forearm on a pillow. A curtain blocked their view of the left forearm and the rest of the room. This was particularly relevant for the Social condition, in which one of two same-sex experimenters applied the social rewards to the participant's left forearm. Two experimenters were always present during testing, to limit the influence of participants' experimenter preferences, and to allow participants to better concentrate on the (social) stimuli.

Participants first completed a short task in which they experienced and ranked by liking all Social and Nonsocial stimuli, presented in semi random order in sets of three stimuli of the same condition. In the main task, which started three hours after pill intake, the previously most liked stimuli were used as 'high' rewards, the stimuli with medium liking as 'low' rewards, and the least liked stimuli were used as 'verylow' rewards. To calibrate the dynamometer, the maximum voluntary contraction (MVC) was established right before the short task, by asking participants to squeeze the dynamometer (HD-BTA, Vernier Software & Technology, USA) with their right hand as hard as possible three times during three seconds.

The average MVC (peak force in newtons across all three trials) was 212 (*SD* = 80.4), and did not differ between Drug groups, as tested by linear regression ($t = .19$, $p = .85$).

After calibration of the dynamometer, EMG electrodes were attached, participants received detailed instructions, and completed four practice trials (two per condition). The main task included four experimental blocks with 20 trials each. Each block contained either food or touch trials, and the blocks were interleaved (ABAB or BABA) in a counterbalanced order across participants. Each trial included (See Fig. 1) the following main steps (see Supporting Information for all elements of a trial): 1) a picture announcing the highest possible reward (high or low, 3 sec), 2) a continuous scale ranging from 'not at all' to 'very much' to rate (without time limit) wanting of the announced reward (ratings were converted to a 20-point Likert scale), 3) a 4-sec period of physical effort, during which probability of receiving the announced reward was determined by the amount of force exerted by squeezing the dynamometer with the right hand, while receiving visual feedback (sliding average of 1 sec, as percentage of the MVC), 4) a picture announcing the obtained reward (3 sec in the nonsocial, 7.3 sec in the social condition), which could be high, low, or – if insufficient effort had been exerted – verylow (the greater participants' effort, the higher the probability of obtaining the announced reward), 5) a phase of reward delivery (2 sec in the food, 6.5 sec in the touch condition – this difference in timing was necessary to obtain sufficiently long tactile stimulation, while keeping the overall trial duration similar across conditions), 6) in the food condition instructions to lean back and swallow the obtained reward (duration 3 sec), 7) a relaxation phase (5 sec), and 8) a continuous scale to rate the liking of the obtained reward. In the food condition, participants then received water for mouth rinsing. In both conditions trials ended with a blank screen for 3 to 4 seconds. The last four trials in each block did not require pressing of the dynamometer – these trials were kept in the data, as removing them from analyses did not change the pattern of results. After each block participants could take a short break.

Both tasks were run on a desktop computer with Windows 7 using MATLAB 2014b and the Cogent 2000 and Cogent Graphics toolboxes, and presented on an LCD monitor with a resolution of 2560 x 1600 pixels. The Positive and Negative Affect Schedule (PANAS) [49] was filled out twice at the main laboratory visit: just before pill intake, and 3 hours later. Levels of amisulpride (ng/ml) were measured in blood samples taken five hours after pill intake (after both tasks).

Analyses

Data were analyzed with linear mixed effects models (LMMs) using the lmer() function of the *lme4* package in R [50,51]. In comparison to ANOVAs, LMMs reduce Type-I errors and allow for the generalization of findings [52]. All the data and analysis scripts are available online (https://osf.io/vu8dz/?view_only=9c99df4e046b4d8796fc0658a9022685). Figures (except Fig. 1) were created in R using the packages *ggplot2, ggpirate,* and *cowplot*.

Behavioral data were analyzed in the following manner. Outlier trials were defined as those with a rating of wanting, rating of liking, or amount of exerted force, which was greater/smaller than the subject's mean +/- 2 times the subject's standard deviation. This led to an average rejection of 6.56 trials per participant (SD = 3.71). The number of excluded trials did not differ between groups, as tested by linear model ($F(2)$ = 2.54, p = 0.08). For each behavioral dependent variable (ratings of wanting and liking, effort), a LMM was run with the fixed effects Condition (food, touch), RewardType (high, low, verylow), and Drug (amisulpride, naltrexone, placebo). Categorical predictors were centered through effect coding, and by-subject random intercepts and slopes for all within-subjects factors and their interactions were included as random effects (unless the model did not converge, in which the slopes by Condition were removed). Type-III F-tests were computed with the Satterthwaite degrees of freedom approximation, using the anova() function of the *lmerTest* package.

Due to technical failure, one participant lacked EMG data entirely, and another participant lacked EMG for half of the trials. EMG data were preprocessed in Matlab R2014b

(www.themathworks.com), partly using the EEGLAB toolbox [53]. A 20 to 400 Hz bandpass filter was applied, then data were rectified and smoothed with a 40 Hz low-pass filter. Epochs were extracted focusing on periods of reward anticipation and reward consumption. EMG was averaged over time-windows of one second, with exception of the 6.5-seconds-long period of touch delivery, which was averaged over five windows of 1.3 seconds each, to reach the same number as for the food condition. We excluded for each participant trials on which the average amplitude in the baseline period of the CS or ZM muscles was lower than M−2*SD, or higher than M+2*SD (M = average amplitude over all trials' baselines for the respective muscle and participant). On average, this led to the rejection of 7.7 % of trials per participant (*SD* = 2.5). EMG analyses were carried out in four periods of interest: *Pre-effort anticipation* during reward announcement at the beginning of each trial (3 sec), *Post-effort anticipation* during the announcement of the gained reward (3 sec), *Delivery* (5 sec in the Food and 6.5 sec in the Touch condition, both averaged to five 1-sec time windows), and *Relax* (5 sec). For each trial, values in these epochs were expressed as percentage of the average amplitude during the fixation cross at the beginning of that trial. For the Pre- and Post-Effort anticipation periods, separate linear mixed-effects models (LMM) were fitted by muscle, with the fixed effects Drug (amisulpride, naltrexone, placebo), Condition (food, touch), and either trial-by-trial Wanting, or Effort (continuous predictors). For the Delivery and Relax periods, separate LMMs were fitted by muscle, with the fixed effects Drug, Condition, and Liking. As failure to receive the announced reward may result in negative emotions and impact the facial expressions accordingly, these trials were included in the analyses of the Pre-effort anticipation window, but excluded from all other analyses windows – although their inclusion did not alter the pattern of results. Wanting, Effort, and Liking were centered and scaled by subject.

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