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CONCISE REPORT

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The role of opioid transmission in music-induced pleasure

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Abstract

Studies conducted in rodents indicate a crucial role of the opioid circuit in mediating objective hedonic reactions to primary rewards. However, it remains unclear whether opioid transmission is also essential to experience pleasure with more abstract rewards, such as music. We addressed this question using a double-blind within-subject pharmacological design in which opioid levels were up- and downregulated by administering an opioid agonist (oxycodone) and antagonist (naltrexone), respectively, before healthy participants (n = 21) listened to music. Participants also performed a monetary incentive delay (MID) task to control for the effectiveness of the treatment and the specificity of the effects. Our results revealed that the pharmacological intervention did not modulate subjective reports of pleasure, nor the occurrence of chills. On the contrary, psychophysiological (objective) measures of emotional arousal, such as skin conductance responses (SCRs), were bidirectionally modulated in both the music and MID tasks. This modulation specifically occurred during reward consumption, with greater pleasure-related SCR following oxycodone than naltrexone. These findings indicate that opioid transmission does not modulate subjective evaluations but rather affects objective reward-related psychophysiological responses. These

findings raise new caveats about the role of the opioidergic system in the modulation of pleasure for more abstract or cognitive forms of rewarding experiences, such as music.

KEYWORDS
music, opioids, pleasure, reward

INTRODUCTION

Experiencing pleasure in response to music is one of the most fascinating abilities we possess as humans. Not surprisingly, there has been a growing interest in understanding the brain mechanisms underlying music-induced pleasure as a window into human brain function in general and complex cognitive and affective processes in particular.[1–3] A large body of neuroimaging research supports the idea that music-induced pleasure relies on the functioning of a set of brain regions involved in reward (e.g., the nucleus accumbens [NAcc], insula, and ventromedial prefrontal cortex) and auditory processing (e.g., the superior temporal gyrus and inferior frontal gyrus) (see Ref. 4 for a meta-analysis on music-induced pleasure). However, although the neuroanatomical correlates of musical pleasure have received most of the attention, its neurochemistry is less understood.

Most of the evidence that we have about the neurochemistry of pleasure comes from animal studies using primary rewards, specifically sweet taste—considered an innate pleasure highly preserved among species and individuals.[5,6] According to a wealth of studies, the opioidergic system causally modulates objective hedonic reactions to sweet taste. Stimulation of opioid receptors (particularly mu-opioid receptors, MOR), in a small group of neurons located along the reward circuitry (called hedonic hotspots), amplifies affective "liking" facial expressions to sweetness (e.g., tongue protrusions[7–9]). Such objective affective reactions are considered core "liking" reactions and do not need to be necessarily perceived as conscious.[6] They reflect in a basic form the "hedonic gloss" glazed onto the sweet sensation, which may later be experienced as conscious pleasure by additional brain mechanisms involved in the conscious and subjective evaluation. However, it is still unclear whether similar neurochemical mechanisms would apply to human pleasure in response to more complex cognitive or aesthetic rewards, such as music.

To the best of our knowledge, three studies have explored the role of opioid transmission in musical reward so far, with mixed results. Back in 1980, Goldstein[10] failed to report a consistent decrease in pleasurable musical chills after the injection of the opioid antagonist naloxone. More recently, using a double-blind within-participants design, Mallik and colleagues[11] showed that blockage of opioid transmission via the opioid antagonist naltrexone reduced subjective reports of pleasure and nonspecific psychophysiological responses (the effects were reported for both pleasant and nonpleasant music). On the contrary, Laeng and colleagues,[12] with a larger sample (49 participants), showed no modulation of subjective reports of pleasure after naltrexone administration but a concurrent decrease in psychophysiological responses (pupil dilation) to musical chills. However, although all these studies included a placebo control condition, they have lacked proper control conditions outside the music domain (e.g., using primary or secondary reinforcers) and active pharmacological controls (i.e., a second drug with either no effect or opposite effects in opioid transmission as an agonist). These limitations do not allow to ensure that the effects reported in these studies were specific to (1) opioidergic manipulation and (2) reward-related responses, rather than drug unspecific general effects in arousal, attention, or motivation due to side effects or merely by the sensation of being under the influence of a drug. Therefore, the role of opioid transmission in musical pleasure remains uncertain.

To fill this gap, we aimed to investigate the contribution of opioid transmission to musical pleasure via a double-blind within-participants design. We orally administered an opioid agonist (oxycodone), antagonist (naltrexone), and a placebo (lactose) in three separated and counterbalanced sessions. Oxycodone is a widely prescribed oral opioid that acts as a selective MOR agonist.[13–16] Naltrexone is a nonspecific competitive opioid antagonist that preferentially blocks MOR, but also kappa and, to a lesser extent, delta-opioid receptors.[17,18] After drug administration, participants performed a well-validated music task that captures subjective hedonic and motivational responses.[19–21] Participants also performed a well-established nonmusic reward task, the monetary incentive delay (MID) paradigm,[22] to control for the specific implication of opioid transmission in the context of a well-known human secondary reinforcer (i.e., money). We also measured skin conductance response (SCR)—considered a reliable, objective indicator of emotional arousal—while participants performed music and monetary tasks. SCR during music listening is modulated by musical pleasure, the intensity of chills experienced, and individual differences in music hedonia,[23–25] representing a good and widely used objective psychophysiological marker of music reward-related processes.

Based on the hypothesis derived from animal research that opioid transmission plays a causal role in the generation of hedonic reactions ("liking" reward component[26]), we predicted that our pharmacological intervention would impact music-induced pleasure, being up- and downmodulated by oxycodone and naltrexone, respectively. In addition, if opioid-induced changes in hedonic processing are specifically observed in objective outcomes during the experience of pleasure, these effects should be particularly evident in pleasure-related SCR changes.

METHODS

Participants

Around 600 individuals were first prescreened by phone. During the prescreening, the main procedures of the study were explained to

confirm individuals' interest in participating. If so, they were asked to indicate if they (1) had any allergy, (2) were taking any medication, (3) presented any chronic disease, (4) frequently consumed drugs, cigarettes, and alcohol, or (5) had musical training. Finally, they were asked to report their preference for several music genres (pop, jazz, classical music, electronic, and others). Of those, 60 passed the prescreening and confirmed their availability. After giving informed consent, they were admitted to the hospital for further screening, medical examination, and laboratory exams (blood test and urinalysis). Volunteers were judged healthy at screening based on medical history, physical examination, vital signs, electrocardiogram, laboratory assessments, negative urine drug screens, negative hepatitis B and C, and HIV serology. Exclusion criteria were: (1) any prescription or over-the-counter medications in the 14 days before screening; (2) medical history of alcohol and/or drug abuse; (3) consumption of over 24 (for female) or 40 (for male) grams of alcohol per day; (4) consumption of over 10 cigarettes/day; (5) lack of efficient contraception methods (for female); (6) positive pregnancy test (for female); (7) allergies; (8) musical training (i.e., participants reporting a formal music education were excluded from the study); and (9) low preference for pop music (since our music selection basically consisted of pop songs, and we wanted to ensure that the participants found them rewarding). Participants were also requested to abstain from alcohol, tobacco, and caffeinated drinks 24 h before each experimental session. Participants received 120 euros for their participation plus the amount of money accumulated in the tasks. The study was approved by the ethics committee of the Hospital de la Santa Creu I Sant Pau and the Spanish Medicines and Medical Devices Agency (EudraCT 2016–000801-35).

Thirty nonmusician volunteers (14 females) were initially included in the study and randomized to the six possible drug-order conditions. Four participants dropped out before the first session, two after the first session, and three more after the second session. None of the dropouts were motivated by adverse effects. Thus, 21 participants (11 females; age = 27 years, SD = 6.76) completed the entire experiment.

Procedures

For each session, participants arrived at the hospital under fasting conditions. They were given a light breakfast after passing drug tests in urine, alcohol breath tests, and pregnancy tests for women. Subsequently, they received in a double-blind masked fashion a capsule containing the treatment: an opioid receptor agonist (oxycodone, 14-hydroxy-dihydrocodeinone, 20 mg, Oxynorm, The Netherlands), an opioid receptor antagonist (naltrexone, N^{17}-cyclopropylmethyl-noroxymorphone, 50 mg, Tranalex, The Netherlands), or placebo (lactose, Fagron, Belgium), counterbalanced across participants. Selected drugs and doses were chosen based on previous studies involving healthy volunteers and investigating reward-related processes. Concretely, the 20 mg oxycodone dose was kept in line with previous studies investigating the role of opioid modulation in reward processing.[16,27] The plasma half-life of oxycodone ranges from 3 to 5 h and is not influenced by the route of administration.[28] The 50 mg naltrexone dose was chosen based on previous studies showing that at this dose, naltrexone effectively blocks subjective rewarding feelings,[29–32] nearly blocks the majority of opioid receptors in the brain,[33] and produces minor side effects in healthy volunteers.[34,35] The dose selected for the antagonist, naltrexone, reaches a peak plasma concentration at 1 h following oral administration.[17,18]

A 3-min SCR baseline (in silence, relaxed, and with open eyes) was recorded 1 h after drug administration. Next, participants performed the music task first and then the MID task (1 h of duration in total) while SCR was recorded. Task order was constant across participants and sessions. After completing the tasks, participants spent their time in a resting room and received light food 4 h after drug intake. They were allowed to leave the hospital after 6 h from the treatment administration. As a security measure, vital signs (heart rate and blood pressure) were evaluated every 30–60 min from the center's arrival until they left. Adverse events reported by the volunteers were also recorded during the study. Seven participants reported moderate adverse effects (from dizziness to nausea)—one with both naltrexone and oxycodone, five with oxycodone only, and one with naltrexone only. At least 1 week passed between one session and the other.

Music task

Participants were asked to listen to 20 musical excerpts in two blocks, one including 10 experimenter-selected songs and the other including the participant's 10 favorite musical excerpts. The order of presentation of both blocks was counterbalanced across participants. During each excerpt (45-s duration), participants had to provide in real-time the degree of pleasure they were experiencing while listening to music by pressing one of four available buttons on a keyboard (1 = no pleasure, 2 = low pleasure, 3 = high pleasure, and 4 = chills). This paradigm has been widely validated in previous studies, showing reliable behavioral, psychophysiological, and neural outcomes.[19–21,23–25] Participants were additionally asked to rate the overall pleasure (from 1 = no general pleasantness to 10 = intense general pleasantness), arousal (from 1 = very relaxing to 5 = very arousing), and emotional valence (from 1 = very sad to 5 = very happy) they felt in response to each excerpt. For the experimenter-selected music, participants were also asked to rate each song's familiarity (from 1 = completely unfamiliar to 4 = I have the song on my PC, mp3, Spotify playlist, etc.). Finally, participants had the opportunity to purchase our music selection using a previously validated auction paradigm,[21,36] in which they were asked to indicate how much money they were willing to spend to buy each musical item (from 0€ to 1.99€). Willingness to pay was an indicator of *wanting*.

Musical stimuli

Stimulus selection followed the procedure of Mas-Herrero and colleagues.[21] Before starting the experiment, participants provided 10 musical excerpts that elicited intensely pleasant emotional responses (45-s duration). These 10 excerpts were presented during all three sessions. In addition, in each session, participants listened to

10 different experimenter-selected pop music excerpts (45-s duration). We selected different excerpts for the three sessions to exclude potential confounding effects of the song's repetition on participants' reward experiences (particularly in the auction paradigm). Therefore, we employed three different pop song lists (i.e., a total of 30 excerpts, 10 excerpts for each list). To ensure that the lists were comparable, we selected three songs from 10 different musical groups or singers and included one on each list. Thus, the three lists contained songs from the same groups/singers (Table S1). As we wanted them to purchase some of these songs during the experiment, we aimed to select slightly familiar songs (i.e., able to induce pleasant reactions) that were not easily recognizable to the participants. To meet this criterion, we selected excerpts from songs in the top 20 in Spain in the last 3 years (http://top40-charts.com/), but without reaching the top 5. Then, we generated the three lists of 10 songs matched by their top 20 positions. The language of the song (i.e., English or Spanish) was balanced within each list. Additionally, we used the Spotify application "Sort your Music" (http://static.echonest.com/SortYourMusic/) in order to match the songs according to different features computed by Spotify's algorithms, namely, tempo, energy, danceability, valence, and popularity (Table S2). Therefore, the three lists were comparable in terms of genre, style, artist, popularity, and acoustic features. The presentation of the three lists was balanced across sessions and participants. All the excerpts were normalized for amplitude (−10 dB) and faded (1 s in and 1 s out). Loudness was subjectively adjusted to a comfortable level for each participant at the beginning of each session and kept constant throughout the experiment.

Monetary incentive delay task

At the beginning of each trial (35 total trials), one of five cue shapes was presented for 2 s. Cues indicated whether they were playing to win potential rewards (14 trials; circle shape) or avoid potential losses (14 trials; square shape). Horizontal lines in the cue signaled the magnitude of the possible outcomes; it could be small (0.1€, one horizontal line, seven trials for each valence) or large (1€, three horizontal lines, seven trials for each valence). Six seconds after cue offset, participants had to respond, as fast as possible, with a button press to a white target square that appeared for a variable length of time (target, 160–260 ms). In win trials, if participants responded on time, they got the corresponding amount of money. If participants responded on time in loss trials, they avoided losing the corresponding amount of money. Feedback notified whether they had won or lost money during that trial 6 s after the participants' response. Eight seconds later, another cue was presented. The task also had a neutral condition (seven trials; triangle shape), in which participants were asked to respond, but no money was at stake. Trial types were randomly ordered within each session. Task difficulty was set such that each participant could succeed on 60% of his/her target responses. Reaction times were collected following each participant's responses, and the reaction time in the 60th percentile of all previous responses was then selected as the threshold for the next trial. Participants' average accuracy in the placebo, naltrexone, and oxycodone conditions was 61.7%, 60.8%, and 62.3%, respectively.

Skin conductance responses

Participants' SCR was recorded during tasks (i.e., music and MID) performance through the Brainvision Brainamp device (Brain Products, Germany). The electrodes were attached to the forefinger and the middle finger of the nondominant hand and placed on the first or second phalange. Before task performance, resting-state baseline data were recorded during 3 min of rest (i.e., resting-state baseline).

For the music task, SCRs associated with low pleasure (ratings 1 and 2) and high pleasure (ratings 3 and 4) were determined by measuring the SCR amplitude after response onset with respect to baseline (−1 s) (see also Ferreri et al., 2019). SCR amplitude was determined in the 0- to 6-s window after participants pressed a button to indicate a change in pleasantness. We only analyzed trials without button responses during the 6-s time window to avoid artifacts from (1) motor responses and (2) the SCR response associated with the subsequent rating (28.9% of trials were excluded on average). Following oxycodone, 22.3 (SD = 8.5) and 14.2 (SD = 5.4) trials were included on average as low and high pleasure conditions, respectively. Following naltrexone, 21.1 (SD = 7.1) and 17.1 (SD = 7.3) trials were included on average as low and high pleasure conditions, respectively. Following the placebo, 19.9 (SD = 5.7) and 17.1 (SD = 6.5) trials were included on average as low and high pleasure conditions, respectively. To obtain the SCR values specifically associated with high pleasurable reactions, SCR from low pleasure ratings was then subtracted from the SCR associated with high pleasure ratings within each session. For the MID task, SCR amplitude was determined in the 0- to 6-s time window after outcome delivery. Trials associated with specific conditions were averaged for each subject.

In each task and for each participant, the resulting SCR amplitude value was normalized across conditions.[24,37,38] We then computed the difference of change under naltrexone and oxycodone with respect to placebo. Cluster-based permutation analysis was carried out to explore differences in placebo-corrected SCR between oxycodone and naltrexone.

Statistical analysis

To investigate the effect of the pharmacological intervention on pleasure, we first estimated each song's pleasure based on participants' real-time ratings while listening to the music, following the same procedure as in Mas-Herrero et al., 2018, 2021.[20,21] Concretely, we performed a weighted average of participants' ratings of pleasure by multiplying the response value—1, 2, 3, or 4—by the duration of each response and dividing it by the total duration. To test the implications of drug-induced opioid modulation on participants' ratings (real-time pleasure, number of chills, overall pleasure, arousal, valence, and amount of money willing to spend), we performed a series of linear

mixed models in R (version 4.0.2) and RStudio (version 1.3.959) using the lme4 package.[39] All models included random intercepts for each subject. Following our main hypothesis, we included as fixed factors the two primary conditions: Drug (oxycodone, placebo, and naltrexone) and music selection (i.e., experimenter- and self-selected), as well as the interaction between the two (to assess whether any potential drug effect was restricted to one particular condition or both). To account for the effects of body weight on the drug dose,[40] we included a three-way interaction between Drug, music selection, and weight. All participants received the same amount of drug, but because they varied in weight, drug doses were different among participants. For that reason, we wanted to assess whether any of the main drug effects tested (Drug and Drug*music selection) could be influenced by the dose received and, consequently, interacted with participants' weight. We also included session order (first, second, and third) to control for any potential unbalance generated by participants' withdrawal since the counterbalancing was initially designed for 30 participants, but 21 completed the entire experiment and considering the reported decline in the intensity of subjective emotional evaluations over time.[41,42] Finally, a factor indicating whether participants reported adverse effects (yes or no) during the experimental session was included in all the analyses to control for its potential effects on performance.[41,42] This led to the following "template" model: Participants' ratings ~ Drug*MusicSelection*Weight + Order + Adverse effects. Familiarity was also included as a fixed factor when investigating monetary bets in only our music selection and not participants' music selection, since participants only had the opportunity to purchase our music selection but not their own. This led to the following model: Monetary bets ~ Drug*Familiarity*Weight + Order + Adverse effects. For all models reported, we followed the same three-step strategy. First, we fit each model with the maximal random effects structure, including subjects' random intercepts, within-subjects random slopes, and their interactions. If the full random structure model did not converge, we then removed correlations between random slopes. Finally, if the resulting model still did not converge, we removed random slopes accounting for the least variance until convergence.[39] The final fixed and random structures of each model can be found in Supporting Information. The effects of the different predictors were then assessed with likelihood ratio tests using the afex package in R. These tests were based on Type 3 sums of squares.

Following a significant interaction, pair-wise post-hoc contrasts with Tukey correction for multiple comparisons were used. Contrasts were carried out using the emmeans package in R. Plots were created using the ggpredict function from the ggeffects package in R. Averaged raw data for the main conditions can be found in the Supporting Information (Figure S1).

RESULTS

We first explored differences across drug treatments in subjective *liking* as reflected by real-time ratings of pleasure while listening to music. Our results show higher subjective reports of pleasure for self- than experimenter-selected excerpts ($\beta = 1.24$, SE = 0.101, $\chi^2(1) = 151.8544$, $p < 0.001$, Figure 1). In addition, real-time ratings were influenced by session order ($\chi^2(2) = 18.25$, $p < 0.001$, Figure S2), with higher ratings during the first session, as compared with the second ($\beta = 0.26$, SE = 0.071, $t = 3.63$, $p = 0.003$), and third ($\beta = 0.26$, SE = 0.07, $t = 3.77$, $p = 0.002$). However, no effect of the Drug ($\chi^2(2) = 1.95$, $p = 0.38$) nor the interaction between Drug and Music Selection or Drug and Weight were found significant (all $ps > 0.40$).

Next, we looked at differences among sessions in the occurrence of more specific and concrete events related to musical pleasure, namely, chills. Therefore, we ran a similar model as in the previous analysis, but now with the number of reported chills on each song as the dependent measure. Consistent with our previous analysis, participants reported more chills with their own favorite music than with our music selection ($\beta = -0.36$, SE = 0.082, $\chi^2(1) = 19.18$, $p < 0.001$, Figure 1). No more effects or interactions were found to be significant (all $ps > 0.2$).

We then explored drug-dependent modulations in the ratings that participants reported after each excerpt (overall pleasure, arousal, and emotional valence). The participants liked more ($\beta = 1.24$, SE = 0.104, $\chi^2(1) = 141.44$, $p < 0.001$), were more aroused ($\beta = 0.87$, SE = 0.111, $\chi^2(1) = 61.77$, $p < 0.001$), and reported to feel more positive emotions ($\beta = 0.57$, SE = 0.127, $\chi^2(1) = 20.25$, $p < 0.001$) with their own excerpts than with the experimenter-selected music (Figure 1). In addition, the appearance of adverse effects was negatively associated with liking rates ($\beta = -0.32$, SE = 0.133, $\chi^2(1) = 5.93$, $p = 0.015$) and arousal ($\beta = -0.45$, SE = 0.136, $\chi^2(1) = 10.81$, $p = 0.001$, Figure S3). Finally, emotional valence was influenced by session order ($\chi^2(2) = 10.48$, $p = 0.005$, Figure S2), with individuals reporting more positive feelings during the first than the third session ($\beta = 0.23$, SE = 0.071, t ratio = 3.15, $p = 0.001$, Figure S2). However, none of these ratings were modulated by the pharmacological intervention (all Drug main effects, Drug*Music Selection, and Drug*Weight interactions with $ps > 0.25$) (Figure 1).

Finally, we investigated the modulatory effect of opioid transmission on *wanting* reflected by the willingness to pay for experimenter-selected music. Familiarity had a positive impact on participants' willingness to pay for our music selection; participants spent more money on familiar music ($\beta = 0.43$, SE = 0.061, $\chi^2(1) = 49.27$, $p < 0.001$, Figure 1). No other effects were found significant.

Given the lack of significant behavioral drug effects, we calculate the Bayes factor to estimate the evidence for the null hypothesis (no effect of the drug) on each analysis. Bayesian analysis indicated no evidence in favor of H_1 (Bf = 1) in monetary bids, and extreme evidence for H_0 in the number of chills, real-time ratings of pleasure, liking, arousal, and emotional valence ratings (all Bf < 1/1000).

We also investigated SCR changes associated with the participants' real-time liking ratings. Specifically, we looked at the time course of the SCR immediately after participants reported experiencing low (ratings 1 and 2) or high pleasure (ratings 3 and 4) while listening to the music and computed the difference between the two as a measure of SCR associated with high-pleasurable states for each session. Next, using cluster-based permutation analysis, we explored differences between the two active sessions (under oxycodone and naltrexone) in placebo-corrected SCR associated with high-pleasure states (as in

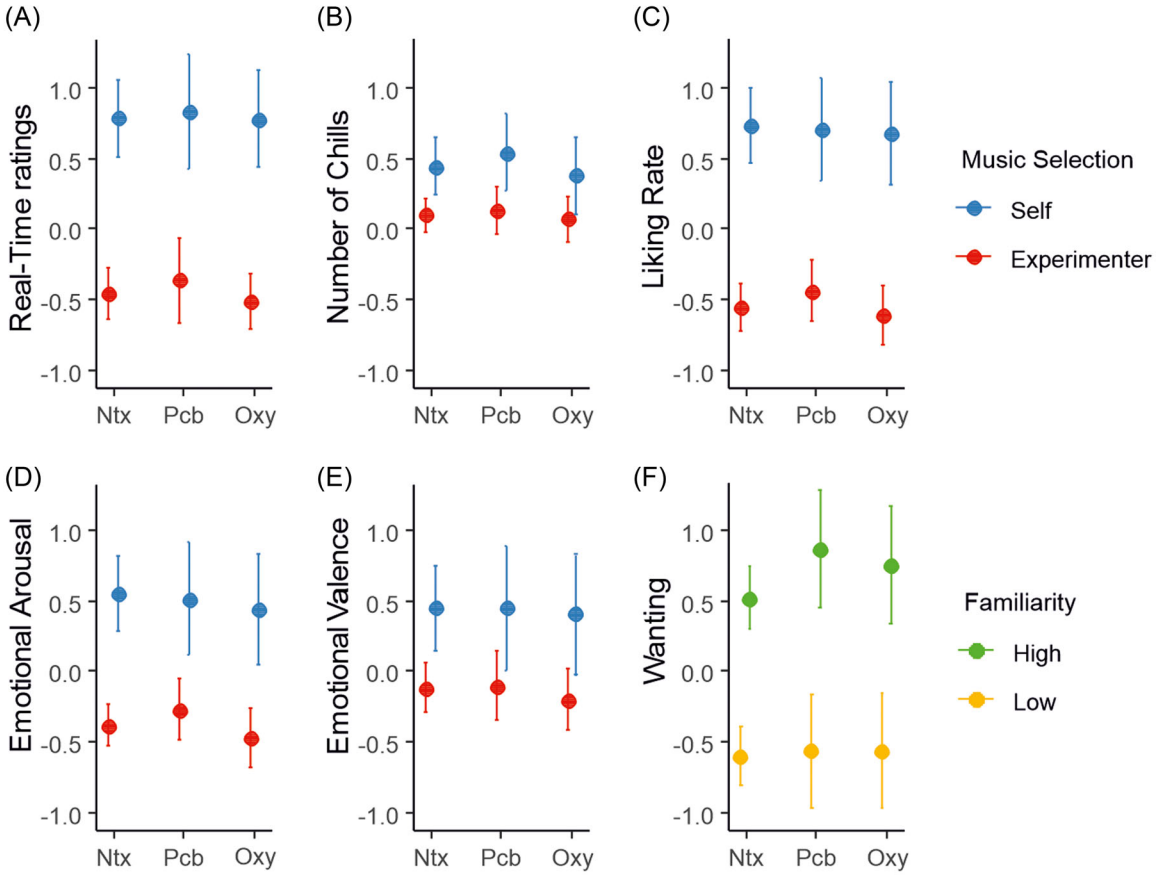

FIGURE 1 Partial effects (with confidence interval) from the linear mixed model analysis parameters, representing the estimated liking based on (A) real-time ratings, (B) the number of chills, and the evaluation of (C) liking, (D) arousal, (E) emotional valence, and (F) wanting after each excerpt as a function of the drug and music selection or familiarity (i.e., for experimenter-selected music only). The intervention did not modulate any of them. Abbreviations: Ntx, naltrexone; Oxy, oxycodone; Pcb, placebo.

Ferreri et al., 2019). The analysis revealed a significant temporal cluster (time-window: 1.67–4.79 s, $p = 0.03$) that differed between the two sessions, with greater SCR amplitude associated with high-pleasure states following oxycodone than naltrexone (Figure 2).

We also investigated any potential drug effect in participants' performance on the MID task. Participants responded faster during the second and third sessions than in the first (order effect: $\chi^2(2) = 9.31$, $p < 0.01$) and when they did not experience adverse effects ($\chi^2(1) = 9.04$, $p < 0.01$). Among the main four conditions (high gain, low gain, high loss, and low loss), they were faster during high gain trials (valence × magnitude: $\chi^2(1) = 4.13$, $p = 0.04$) and more accurate during high magnitude trials (magnitude: $\chi^2(1) = 9.18$, $p < 0.01$). None of these effects interacted with the Drug (all $ps > 0.1$). However, individuals were overall faster in placebo sessions than after administration of naltrexone (Drug: $\chi^2(2) = 14.70$, $p < 0.001$; Placebo vs. Naltrexone: $t = -3.83$, $p < 0.001$).

Next, we also investigated SCR associated with monetary rewards. Cluster-based permutation analysis revealed a drug-dependent modulation effect in the SCR's amplitude associated with high versus low monetary gains. SCR associated with high monetary reward was greater following oxycodone than naltrexone (from 0 to 4.33 s, $p = 0.03$, Figure 2). Notably, no significant differences were observed between the two drugs in the high versus low monetary loss contrast (Figure S4), during the neutral (i.e., nonrewarding) condition of the MID, nor during the 3-min pretasks baseline period (all $ps > 0.25$), providing evidence about the specificity of the drug modulation on reward processing.

DISCUSSION

The current study aimed to investigate the causal role of opioid transmission in music-induced pleasure. Our results revealed that the pharmacological intervention up- and downmodulated pleasure-related psychophysiological responses (i.e., SCR) following oxycodone and naltrexone, respectively. However, no effects were observed in real-time subjective ratings of pleasure or hedonic feelings, nor the occurrence of pleasurable chills.

Over the past decades, animal studies have shown that particularly mu, but also delta, and kappa opioid stimulation in a specific group of neurons in the NAcc (hedonic hotspots) can at least double the hedonic impact of sucrose.[8,26,43] Previous human studies also showed clear effects of opioid signaling for hedonic responses to food and

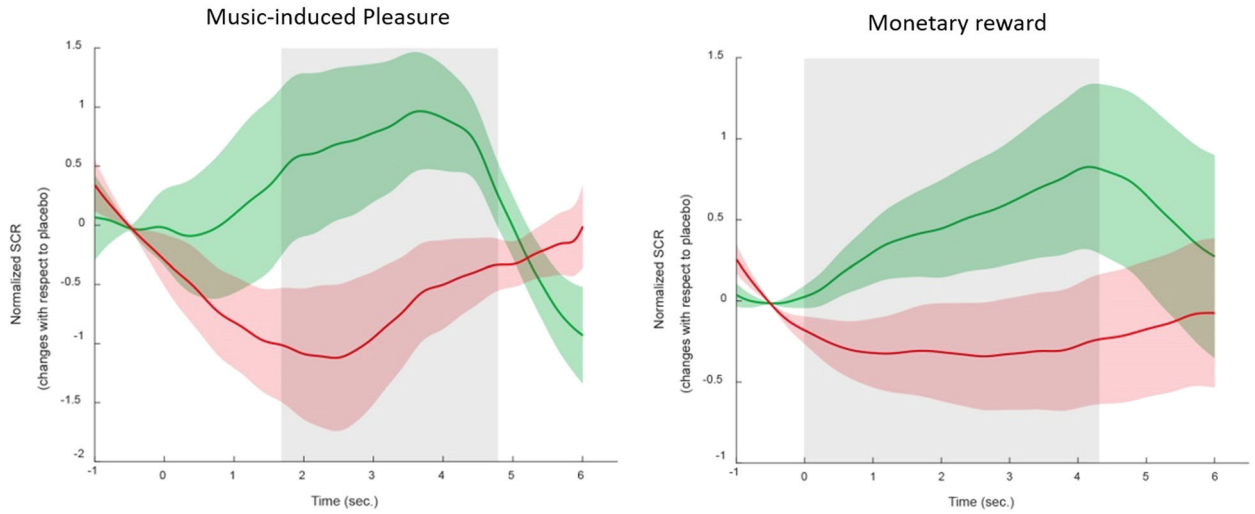

FIGURE 2 Placebo-corrected SCR changes (means, solid lines ± SEM, lighter colors) associated with (A) high-pleasurable states during music listening; and (B) high-monetary outcomes in the MID control task, under oxycodone (green) and naltrexone (red). Gray blocks indicate the significant clusters that differ between sessions.

taste pleasantness,[44,45] erotic stimuli,[46] monetary reward,[47] and facial attractiveness[29] (see for a recent review Ref. 48). Yet, less is known about the role of opioids in abstract, aesthetic rewards.

We did not observe any impact of opioids on the subjective hedonic ratings for music listening. This result converges with recent findings in which no modulation of subjective hedonic responses to music[12] or social touch[30] was observed following opioid antagonist (naltrexone) administration. Also, subjective reports of music-induced pleasure were not particularly impaired in alcohol-dependent patients after long-term repeated administration of intramuscular naltrexone.[49] The present findings also resonate with current theories of opioids' role in food reward that posit that opioid-dependent hedonic signals may not necessarily serve as input to the cognitive and subjective evaluation needed to experience conscious feelings of pleasure, which may depend on other neural circuitries, including mesolimbic dopaminergic pathways.[26,50–52]

However, we did observe a clear modulation of opioid neurotransmission on pleasure-related psychophysiological responses: increasing and decreasing opioid transmission up- and downregulated SCR responses associated with musical pleasure, respectively. Human studies investigating music-induced reward have generally used SCR as an objective marker of hedonic-related processes.[24,25,53] Indeed, SCR during music listening is modulated by experienced pleasure, particularly rising following the occurrence of chills. In addition, the SCR amplitude following musical chills predicts the intensity of chills and reflects individual differences in music hedonia.[24,25] Therefore, while opioidergic stimulation did not change subjective hedonic levels, it did effectively modulate pleasure-related psychophysiological measures.

Similar dissociations between subjective hedonic measures and involuntary objective psychophysiological measures have been previously observed for opioid neurotransmission in music listening[12] (using pupil dilation to chills) and social touch[30] (reduction in positive facial reactions to liked rewards). Similarly, animal studies investigating food reward have also shown modulation of involuntary facial affective expressions to sweet taste following alterations of the opioid hedonic circuitry.[5]

Importantly, we obtained similar findings in the monetary reward control task: administration of the opioid agonist oxycodone was associated with SCR increases for high- versus low-magnitude monetary gains (but not losses), and this response decreased under the opioid antagonist naltrexone. SCR associated with neutral trials, in which participants did not lose or win money, was not modulated by the drug. In parallel, SCR values did not differ across drug sessions at baseline (recorded during 3 min of silence, relaxation, and eyes open before starting the music task). The results in these control conditions further confirm the effect of opioid neurotransmission in modulating reward-related psychophysiological responses, thereby validating our pharmacological intervention's effectiveness and ruling out any unspecific drug or task effect.

Notably, and in contrast to our results with drug-induced opioid modulation, we have previously shown that modulation of dopaminergic function can lead to changes in real-time ratings of pleasure and the number of experienced chills.[19] These complementary findings may indicate that while dopaminergic transmission may affect subjective peaks of pleasure and the occurrence of chills in music, opioid transmission is specifically involved in regulating psychophysiological responses associated with those peaks of pleasure without necessarily altering subjective feelings. Thus, the dopaminergic function could constitute a bottleneck or a gateway to musical pleasure (i.e., facilitating the occurrence of chills), although the corresponding physiological reactions may ultimately depend on opioid transmission. Indeed, humans'unique cognitive capacity may have provided alternative ways to trigger opioid-dependent hedonic signals expanding the

range of events and experiences that we may find pleasurable. In fact, most of the cognitive computations involved in music reward are driven by dopaminergic transmission: such as learning, anticipation, memory, or attention.[54–57] It is then plausible that the correct functioning of these dopamine-dependent processes may determine the entry of highly processed auditory information into the opioid circuitry. However, to have a clearer understanding of the interplay between these two neurotransmitter systems in musical pleasure, further pharmacological studies are necessary. These should involve manipulations of both neurotransmitters simultaneously or/and in combination with positron emission tomography to measure the actual release of either opioids or dopamine in reward-related structures. Finally, including taste reactivity tests to measure innate pleasure reactions to sweetness would be critical to further investigate potential music-specific reward mechanisms, particularly those involving the dopaminergic system. Nevertheless, a key challenge is that tasks developed to assess reward-related responses to primary (e.g., sweetness), secondary (e.g., money), and abstract (e.g., music) rewards differ in terms of sensory processing, cognitive demands, and task structure. Indeed, generally, they only have in common their rewarding nature. Therefore, although a direct comparison between them might represent a good model to investigate common reward mechanisms, these differences might hinder the assessment of reward-type specific mechanisms. In this regard, new experimental models and designs are required to explore differences between abstract and primary pleasures, teasing apart all inherent confounders.

The present findings provide new insights into the neurochemistry of complex cognitive and abstract rewards, especially regarding the dissociation between subjective pleasure and objective psychophysiological measures. By including control tasks related to reward processing outside the music domain and active pharmacological controls, our results indicate that opioid transmission might regulate pleasure-related psychophysiological responses; but that these effects might not be easily read out at higher-cognitive levels, as at the level of subjective pleasure judgments. Our findings also have important implications considering that opioids are a widely prescribed analgesic drug despite their highly addictive properties. Showing that psychophysiological hedonic reactions in music depend on opioid transmission could open new perspectives for musical interventions in standard care to reduce opioid consumption (e.g., in chronic pain treatment).

AUTHOR CONTRIBUTIONS

E.M.-H., L.F., J.R., and A.R.F. designed the research. R.M.A. provided logistical support. E.M.-H., G.C., M.V., L.F., and F.P.-J. performed the research. E.M.-H. analyzed the data. E.M.-H., L.F., G.C., E.M.-H., R.J.Z., and A.R.-F. wrote the paper.

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COMPETING INTERESTS

The authors declare no competing interests.

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