Supporting Information

Article: **"Dopamine modulates the reward experiences elicited by music"**

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Participants prescreening and selection

Around 150 individuals responded to advertisements and were contacted for a first phone pre-screening. Of those, 45 confirmed their availability and, after giving informed consent, were admitted at the hospital for further screening, medical examination and laboratory exams (blood and urinalysis). Subjects were judged healthy at screening 3 weeks before the first dose based on medical history, physical examination, vital signs, electrocardiogram, laboratory assessments, negative urine drug screens, and negative hepatitis B and C, and HIV serologies. The volunteers were excluded if they had used any prescription or over-the-counter medications in the 14 days before screening, if they had a medical history of alcohol and/or drug abuse, a consumption of more than 24 or 40 grams of alcohol per day for female and male, respectively if they smoked more than 10 cigarettes/day. Women with a positive pregnancy test or not using efficient contraception methods and subjects with musical training or those unable to understand the nature and consequences of the trial or the testing procedures involved were also excluded. Additionally, volunteers were requested to abstain from alcohol, tobacco and caffeinated drinks at least during the 24 h prior to each experimental period. A sample size of 30 was selected based on several criteria, including the recommendation that, in order to achieve 80% of power, at least 30 participants should be included in an experiment in which the expected effect size is medium to large (1). We also computed a sample size analysis using the G*Power program, which showed that a sample size of 28 was required to ensure 80% of power to detect a moderate effect (0.25) in a repeated-measures ANOVA with three sessions at the 5% significance level.

Drugs and doses

The dopaminergic system has a physiological or intrinsic state whose effects are most likely reflected by the values of the dependent variables measured during the placebo session. In this study, we intended to lower and raise this baseline dopaminergic state by means of two independent pharmacological interventions involving low-to-moderate doses of levodopa (levodopa, 100 mg + carbidopa, 25 mg) and risperidone (2 mg). Drug doses were carefully chosen to be low enough to induce the desired modulation but not too large to allow collateral effects to become a confounding factor. In particular, the levodopa dose was kept in line with

previous studies in healthy participants and within the dose range administered in clinical practice for the treatment of Parkinson's disease and in the cognitive literature (2-6). A higher dose could have led to an unacceptable higher risk of adverse events (e.g., dangerous decreases in blood pressure, intense nausea and vomiting, prominent general discomfort). Regarding risperidone, we selected the dose based on the recommendation from the product summary information to avoid as much as possible the well-known sedative effects risperidone can induce in healthy volunteers while having an effect on dopamine system, as shown in previous studies (see also 7-9). In our study, the self-reported sedative effect was mild and occurred after the music reward task was evaluated. No other side effects affecting participants' well-being nor threatening the experimental session, and more specifically the musical reward task, were reported.

The purpose of this study was to elucidate whether modulation of the dopaminergic system influenced the variable under study (i.e., music-related reward hedonic and motivational responses), rather than to assess the capacity of the drugs themselves to block or enhance the natural physiological responses influenced by dopamine. Levodopa and risperidone were chosen to "displace" the baseline physiological system in opposite directions: risperidone to lower the effects of physiological dopamine release and levodopa to enhance dopaminergic neurotransmission. Thus, as the objective was to bring the dopaminergic system away from its intrinsic state (i.e., the placebo session) and in opposite directions, our analyses focused in directly comparing the risperidone and levodopa data against each other by using the placebo session as a baseline (see fig.1 of the paper).

Motivational ratings: the auction paradigm

For each experimenter-selected song, participants could indicate whether they were willing to pay €0, €0.29, €0.99, €1.29. Each participant was given a budget of €3.87 (€1.29 per session, i.e. the maximum value of a song). At the end of each session, one excerpt was randomly selected. If their bid was the same or higher than the real price of the song (randomly assigned at the beginning of the experiment, ranging from $0.29 to €1.29, and unknown to the participants), they would get a legal copy of the song at the end of the experiment. In that case, the amount of money they were willing to pay was discounted from the initial budget. In contrast, if their bid was lower than the assigned price, they would not get the song, but keep the money. As for (10, 11), the rules of the auction create a situation in which the optimal strategy for the individual is to bid exactly what they are willing to pay for a given item, in this way avoiding bias related to sequentially bidding. Participants did not have to worry about spreading their budget over the different items, but could treat each excerpt as if it was the only decision that counted. At the end of the experiment, participants received the remaining budget in addition to the budget accorded for the participation in the experiment. As they could keep the amount that was not spent, they were spending their own money on music (see 10).

Musical stimuli

Stimuli selection followed the procedure of Mas-Herrero and colleagues (11). Participants were instructed to provide the names (or the internet links) of five musical excerpts that usually elicit intensely pleasant emotional responses for them (duration of 45 sec). They were exposed to these five excerpts during all three sessions. In addition, in each session, participants listened to ten different experimenter-selected pop music excerpts (also duration of 45 sec). In order to exclude potential confounding effects of the songs repetition on participants' reward experiences (e.g., increases in chills or bid responses), different excerpts were selected for the three sessions. This led to three different lists of pop songs (with 10 excerpts for each list, for a total of 30 excerpts). To ensure that the lists of songs were comparable across session, we selected these thirty songs from ten different musical groups, most of them pop bands (three songs for each group). There was a different song from each group at each session (ten in total, see Table S1). In the experimenter-selected list we aimed to select songs that were slightly familiar (to ensure pleasant reactions) but not easily recognizable for the participants, as we wanted them to purchase these songs during the experiment. In order to meet this criterion, we selected excerpts that were, in the last three years, in the top 40 in Spain (http://top40-charts.com/) but without reaching the top 5. Then, we generated the three lists of 10 songs matched by their top 20 position. The language of the song was balanced within each list, with 5 songs in Spanish and 5 in English. Additionally, using the Spotify application "Sort your Music" (http://static.echonest.com/SortYourMusic/), we matched them according to different features computed by Spotify's algorithms, namely bpm, energy, danceability, valence, and popularity (see Table S2). The presentation of the three lists of experimenter-selected songs was randomized and balanced across sessions and participants. All the excerpts were normalized (-10dB) and faded (5 seconds in and 5 seconds out). Their loudness was subjectively adjusted at the beginning of each session and kept constant throughout the whole experiment.

Analysis of behavioural ratings

The percentage of change under risperidone and levodopa with respect to placebo session was computed for each measure. Chills rates were analyzed for N=16, namely the number of participants reporting chills during placebo session. Chills were defined according to participants' ratings (i.e. 4), lasting from 1 to 10 seconds. One subject (participant n.4) showed an anomalous behavioral pattern, reporting real time ratings for less than 50% of the overall listening time for certain songs and no ratings at all for the others. We therefore excluded this participant from the analysis of the real-time ratings, therefore analyzed for N=26. Placebo-corrected values of real-time ratings, as well as the total time reporting real-time ratings, were then compared between pharmacological interventions (i.e., risperidone and levodopa) using Wilcoxon Signed-Ranks Test for paired samples. Wilcoxon non-parametric tests were also employed to compare pharmacological interventions for the ratings provided after each song (i.e., general pleasantness rate, arousal, emotional valence, familiarity, bids). Since all behavioral ratings are provided in an ordinal scale, the use of non-parametric tests is preferred for

these analyses. One subject (participant n.1) presented % of change in motivational responses greater than 5 standard deviation from the mean and another (participant n.6) did not provide any bid at placebo condition. They were therefore excluded from the analysis of the wanting rate (N=25). The general drug effect (fig. S4, S5) was computed as the difference between percentage of change with respect to placebo under levodopa and percentage of change with respect to placebo under risperidone. Wilocoxon Signed-Ranks Tests were employed to test for differences in general drug effect values associated to real-time between self- and experimenter-selected music. Kruskal-Wallis H Tests for independent samples were employed for assessing whether general drug effect values associated to both pleasure (i.e., real-time ratings) and motivational (i.e., bids) reward responses were affected by gender differences (i.e., males versus females).

Electrodermal activity (EDA) recording and analysis

EDA was recorded through Brainvision Brainamp device during task performance. The electrodes were attached to the forefinger and the middle finger of the non-dominant hand and placed in the first or second phalange. Baseline physiological data were recorded during three minutes of rest (i.e. resting state baseline) prior to the task. EDA was analyzed by computing the proportion of change of EDA amplitude following stimulus or response onset, compared to the baseline period (-500 ms). The subject (participant n.4) was excluded from the behavioral analysis of liking rate and the same participant was also excluded from EDA analysis associated to real-time behavioral ratings. In the music task, EDA for each rating – NP, LP, HP, chill - was determined by measuring the EDA amplitude after response onset with respect to baseline (−500 ms). EDA amplitude was determined in the 0- to 7-s window after participants pressed a button to indicate a change in pleasantness. Previous studies have shown that EDA during this time window is modulated according to the degree of pleasure experienced (12, 13). Given the small number of no-pleasure ratings (on average, fewer than 4 ratings per session) and chills (on average, fewer than 3 ratings per session, see also 14), no-pleasure and low-pleasure ratings were grouped into one condition (low pleasure) while high-pleasure and chills were grouped into another (high pleasure). The two conditions had similar amount of trials but were associated with different degree of pleasantness, low and high respectively. In order to obtain the EDA values associated to high pleasurable responses, EDA associated to low pleasure on-line ratings (i.e., 1 or 2) was then subtracted from the EDA associated to high pleasure on-line ratings (i.e. 3 or 4). For the MID task, EDA amplitude was determined in the 0 s to14 s windows after cue onset, i.e. the window corresponding to the anticipation to potential rewards or neutral outcomes. Trials associated with specific conditions were averaged for each subject. In each task and for each participant, the resulting EDA amplitude value was normalized across conditions. The difference of change under risperidone and levodopa with respect to placebo was then computed for these normalized values. Paired-sample t-tests were then run for comparing placebo-corrected values between pharmacological sessions.

Artist	Lang	Songs List 1	Songs List 2	Songs List3
Alejandro Sanz	Spa	Camino de rosas	Mi marciana	Capitán tapón
Amaia Montero	Spa	Caminando	Darte mi vida	Palabras
Antonio Orozco	Spa	Estoy hecho de pedacitos de ti	Hoy será	Mírate
Auryn	Eng	Electric	Heartbreaker	I'll reach you
Birdy	Eng	Skinny love	People help the people	Wings
Katy Perry	Eng	Dark horse	Firework	Walking on air
Maldita Nerea	Spa	Mira dentro	Hecho con tus sueños	Buena energía
Melendi	Spa	Canción de amor caducada	Más allá de nuestros recuerdos	Tu jardín con enanitos
One Direction	Eng	Steal my girl	Infinity	You & I
Taylor Swift	Eng	Bad blood	We are never getting back together	I know you were trouble

Table S1. Titles of the three lists of experimenter-selected pop songs, together with corresponding artist and language (Spa for Spanish, Eng for English), employed in the three different pharmacological sessions.

	List 1		List 2		List 3		*p* values
BPM	122.9	(32.67)	117.6	(26.48)	132.9	(36.51)	.620
Energy	65.3	(18.48)	71.9	(16.47)	71.4	(19.79)	.652
Danceability	62	(12.31)	62.5	(10.69)	57.6	(8.81)	.335
Valence	52.1	(22.94)	48.8	(20.93)	51.2	(19.91)	.928
Popularity	52.1	(16.88)	48	(14.53)	50.2	(15.77)	.718

Table S2. Mean (and standard deviations) and *p* values resulting from repeated measures ANOVA for Spotify's algorithms of bpm, energy, danceability and valence obtained with the Spotify application "Sort your Music".

Volunteer	Sequence	Treatment Order
1	5	B / A / C
2	4	A / C / B
3	5	B / A / C
4	6	C / B / A
5	2	B / C / A
6	2	B / C / A
7	2	B / C / A
8	6	C / B / A
9	1	A / B / C
10	5	B / A / C
11	3	C / A / B
12	5	B / A / C
13	3	C / A / B
14	4	A / C / B
15	1	A / B / C
16	1	A / B / C
17	2	B / C / A
18	5	B / A / C
19	1	A / B / C
20	3	C / A / B
21	4	A / C / B
22	6	C / B / A
23	4	A / C / B
24	6	C / B / A
25	6	C / B / A
26	3	C / A / B
27	1	A / B / C
28	4	A / C / B
29	2	B / C / A
30	3	C / A / B

Table S3. Counterbalancing across treatments, with six different sequences of letters randomly assigned to N=30. A corresponded to risperidone, B to placebo and C to levodopa. Treatment-letter assignment has been performed randomly by a member of the Biometrics department of Sant Pau Hospital, who kept the record unavailable to the investigators until finalization of the experimental sessions.

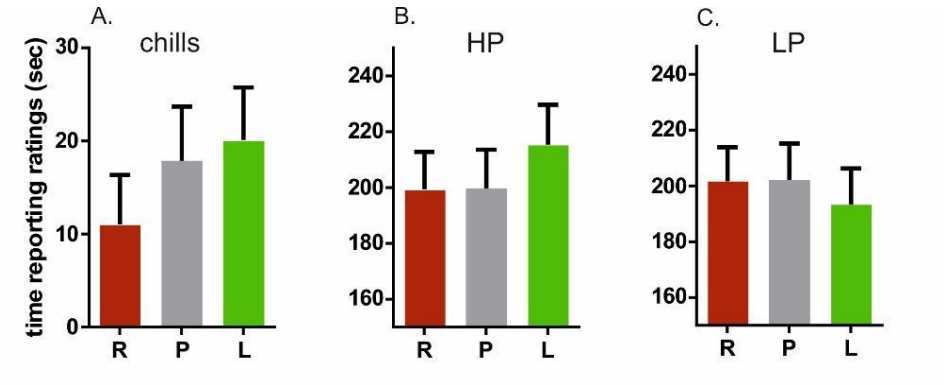

Fig. S1 Bars (means ±SEM) indicating the total amount of time (in seconds) reporting real-time ratings while listening each song: chills (A, chills responders only), high pleasure (B, whole sample), and low pleasure (C, whole sample), under risperidone (R, red), placebo (P, grey) and levodopa (L, green). No pleasure ratings did not show significant differences when comparing placebo-corrected risperidone vs levodopa values.

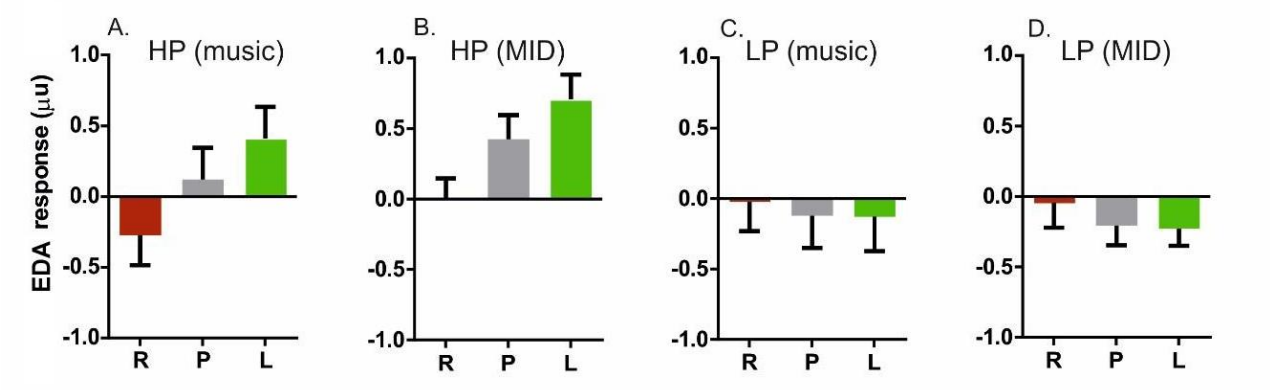

Fig. S2 Bars (means ±SEM) indicating EDA responses corresponding to high and low pleasure while listening to music (A, B) or during MID task (C, D) under risperidone (R, red), placebo (P, grey) and levodopa (L, green).

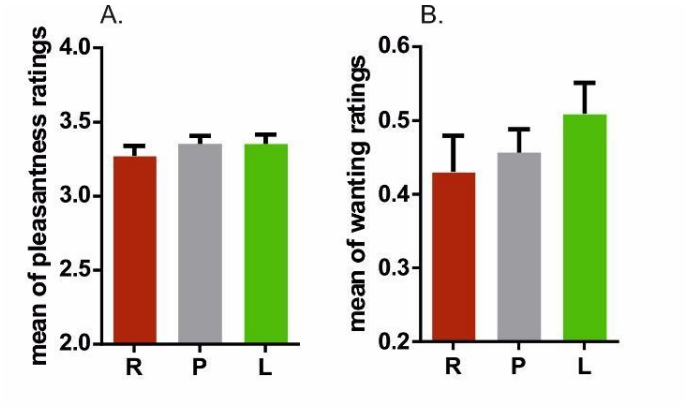

Fig. S3 Bars (means ±SEM) indicating the mean of subjective ratings provided after each song: pleasantness ratings (A) and wanting measure (i.e., money subjects were willing to spend for each song, B) under risperidone (R, red), placebo (P, grey) and levodopa (L, green).

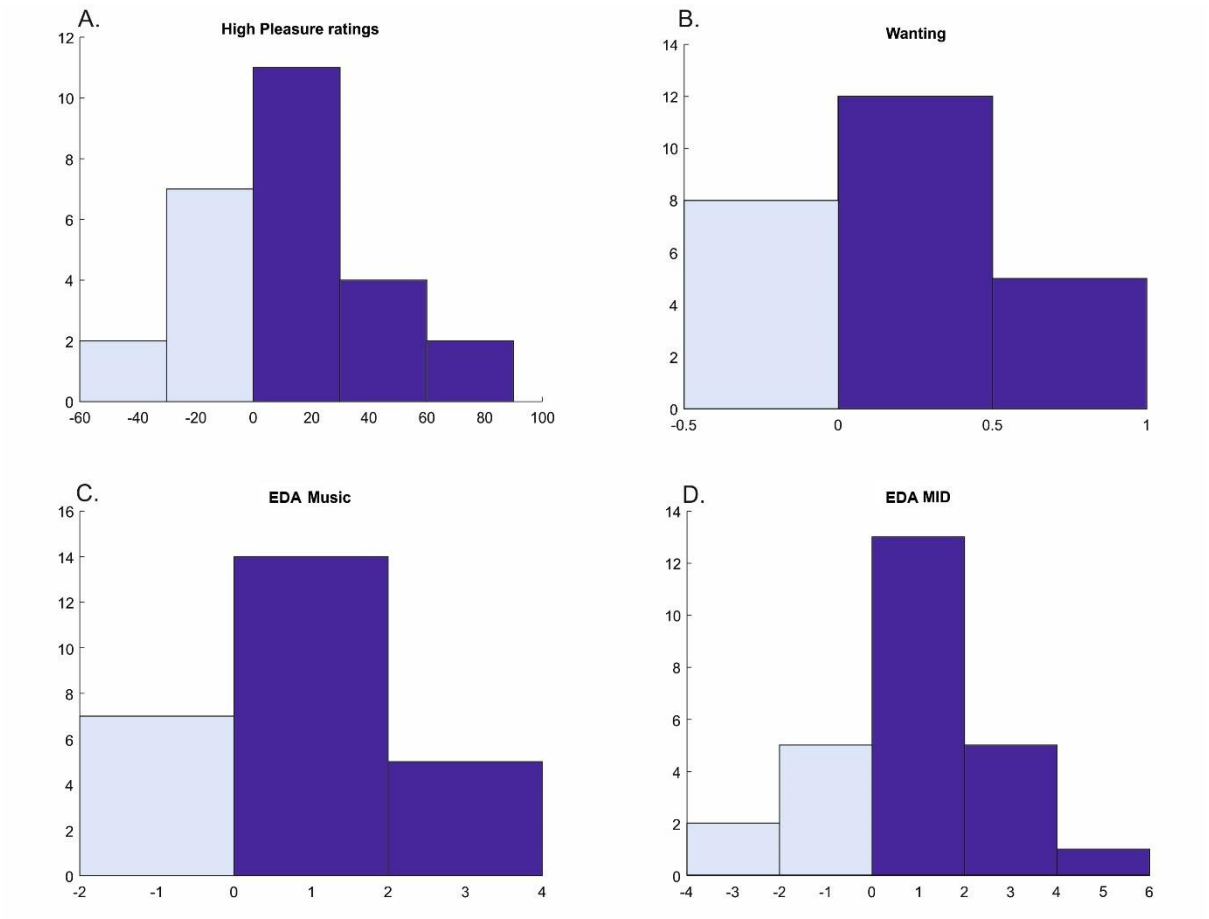

Fig. S4 Distribution of the difference between percentage of change with respect to placebo under levodopa and percentage of change with respect to placebo under risperidone (i.e., general drug effect) for high pleasure real-time rates (i.e. liking, A), wanting rates (i.e., the amount of money participants were willing to pay, B), and EDA response during music listening (C) and MID task (D). Positive numbers indicate a change in the

predicted direction between levodopa and risperidone (light blue bars); negative numbers indicate a change in the opposite direction (blue bars). Note that in all cases the distribution is shifted to the right (positive values), with most of the participants showing an increase under levodopa with respect to risperidone (blue bars).

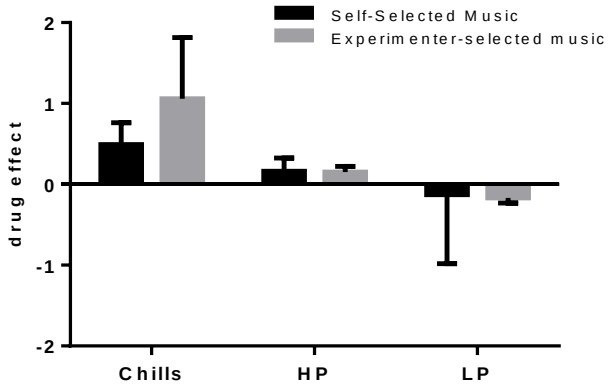

Fig. S5 General drug effect (i.e., % change under levodopa - % change under risperidone) for both self-selected (i.e., favorite) and experimenter-selected (i.e., pop) music for real-time ratings where differences between pharmacological interventions resulted significant (i.e., chills, high pleasure -HP-, and low pleasure -LP-). No significant differences were found according to music selection.

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