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Dopamine modulations of reward-driven music memory consolidation

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Music listening provides one of the most significant abstract rewards for humans because hearing music activates the dopaminergic mesolimbic system. Given the strong link between reward, dopamine, and memory, we aimed here to investigate the hypothesis that dopamine-dependent musical reward can drive memory improvements. Twenty-nine healthy participants of both sexes provided reward ratings of unfamiliar musical excerpts that had to be remembered following a consolidation period under three separate conditions: after the ingestion of a dopaminergic antagonist, a dopaminergic precursor, or a placebo. Linear mixed modeling of the intervention data showed that the effect of reward on memory—i.e., the greater the reward experienced while listening to the musical excerpts, the better the memory recollection performance—was modulated by both dopaminergic signaling and individual differences in reward processing. Greater pleasure was consistently associated with better memory outcomes in participants with high sensitivity to musical reward, but this effect was lost when dopaminergic signaling was disrupted in participants with average or low musical hedonia. Our work highlights the flexibility of the human dopaminergic system, which can enhance memory formation not only through explicit and/or primary reinforcers but also via abstract and aesthetic rewards such as music.

Keywords: music; memory; reward; dopamine; pleasure

Introduction

Music is among the most rewarding stimuli in humans' lives, able to consistently modulate the activity of core reward regions within the mesolimbic dopaminergic system.[1–8] Interestingly, humans show significant individual differences in sensitivity to musical reward, and this variance is related to both brain structure and function of the reward circuitry.[9–14] Although acting via similar circuitry as

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primary rewards, such as food or sex, music does not apparently provide clear survival advantages. This raises interesting questions about the nature of music reward–related signals and their relationship with other core cognitive functions.

In this vein, pleasure (i.e., the hedonic component of reward, together with the wanting and learning aspects[15]) is intimately related to other important aspects of cognition, such as learning and memory.[16–18] Not only primary and secondary (e.g., money[19]) but also higher-order abstract rewards[15] promote memory formation. Improvements in memory performance have been related to higher levels of curiosity,[20] and even intrinsic reward in the context of self-regulated learning.[21,22]

Although several studies have indicated that music can be a powerful enhancer of memory,[23] two fundamental questions are (1) Which specific brain mechanisms underpin such memory benefits? and (2) How can the differences in music effect on memory across subjects be explained?[24] The hypothesis we aim to explore in this paper is, that dopamine-dependent musical reward can drive memory improvements.

In previous work we experimentally drove this theoretical framework by collecting subjective ratings of pleasure from participants who listened to unfamiliar pieces of classical music and were later tested for episodic memory of the pieces. The behavioral results indicated that music reward and memory are intimately related: the greater the pleasure elicited by a particular song, the better the memory for that particular musical piece after a consolidation period (24 hours). The strength of this effect varied depending on participants' sensitivity to musical reward (i.e., their musical hedonia[9]): the higher the musical hedonia scores, the better the musical memory.[25] Exploration of the brain mechanisms underpinning this music reward–driven effect on memory was not included in our previous study, however, owing to its behavioral focus.

Pharmacological interventions are useful for investigating neurochemical mechanisms such as the causal implications of dopamine-dependent signals in learning and memory processes. Increasing synaptic dopamine concentration via d-amphetamine, methylphenidate (i.e., dopamine reuptake blockers), or levodopa (i.e., a dopamine precursor) can effectively enhance learning and memory performance.[26–30] Also, dopaminergic manipulation modulates affective responses to music.[8]

Here, we investigated whether dopamine plays a causal role in reward-potentiated music memory through a double-blind, within-subject pharmacological design in which we directly manipulated synaptic dopamine availability. Participants listened to unfamiliar music excerpts after orally ingesting a dopamine precursor (levodopa), a dopamine antagonist (risperidone), or a placebo across three sessions. Music reward responses were measured by asking participants to provide subjective pleasure ratings after each musical excerpt. Ratings for arousal and emotional valence were also collected as a control. Participants' sensitivity to musical reward (i.e., individual musical hedonia) was obtained via the Barcelona Music Reward Questionnaire (BMRQ[9]). Episodic memory performance for the presented songs was tested 24 h after encoding using a recognition–recollection paradigm.[31]

We hypothesized that because reward-potentiated music memory is a dopamine-dependent mechanism, pharmacological intervention should modulate the relation between pleasure (i.e., subjective ratings) and memory performance, as a function of individual differences in musical hedonia.

Materials and methods

Participants

Participant selection was previously described in Refs. 8 and 32 (participants are the same as in these two other studies). Around 150 individuals responded to advertisements and were contacted for a first phone prescreening. Of those, 45 confirmed their availability and were admitted to the hospital for further screening, a medical examination, and laboratory examinations (blood and urinalysis).

Subjects were judged to be 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, had a medical history of alcohol and/or drug abuse, consumed more than 24 or 40 g of alcohol per day

for females or males, respectively, if they smoked more than 10 cigarettes per day, or if their body mass index was $\leq$19 or $\geq$28. Women with a positive pregnancy test or not using efficient contraception methods, participants with musical training, and 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 for at least 24 h before each experimental period.

Twenty-nine volunteers completed the study (19 females, mean age = 22.83 $\pm$ 4.39 years). All participants gave informed written consent and received compensation for their participation in the study according to Spanish legislation. The initial sample size was chosen to be 30 participants, but one participant dropped out early in the study and only 29 completed it. This sample size was selected based on the sample sizes of previous studies using levodopa to modulate memory (range: between 10 and 30 participants[28,30,33–35]). Selected participants were also tested with the BMRQ,[9] which is able to measure the individual's sensitivity to musical reward (i.e., musical hedonia) and to explain individual differences in brain structure and function in response to pleasurable music.[9–11,14] We employed here an extended version of the BMRQ, including two items testing for amusia (see also Ref. 8). Furthermore, participants were tested with the physical anhedonia scale (PAS[36]). No participants presented signs of amusia. Two participants scored within the ranges considered to indicate musical anhedonia and general anhedonia, and two other participants performed very poorly in the memory task, and they were all, therefore, excluded from the analysis reported here. Furthermore, four participants were also excluded as they consistently identified as familiar with the songs presented during the three sessions (less than 25% of available trials left after discarding familiar musical pieces; total n = 21, 15 females, mean age = 22.28 $\pm$ 4.00 years, mean BMRQ = 77.57 $\pm$ 9.58).

Experimental design

This double-blind, crossover, treatment sequence–randomized study[8,32] was performed at the Neuropsychopharmacology Unit and Center for Drug Research (CIM) of the Santa Creu i Sant Pau Hospital of Barcelona (Spain). This study was performed according to local ethics regulations and the Declaration of Helsinki. It was approved by the Ethics Committee of Hospital Sant Pau and the Spanish Medicines and Medical Devices Agency (EudraCT 2016-000801-35).

Experimental testing took place over three sessions (i.e., interventions; Fig. 1). For each session, participants arrived at the hospital under fasting conditions and were given a light breakfast. Subsequently, they received in a double-blind masked fashion a capsule containing the treatment: a dopaminergic precursor with an inhibitor of peripheral dopamine metabolism (levodopa, 100 mg + carbidopa, 25 mg), a dopamine receptor antagonist (risperidone, 2 mg), or a placebo (lactose). In contrast with methylphenidate and d-amphetamines, levodopa does not indiscriminately enhance tonic dopamine levels but is rather rapidly taken up by dopaminergic neurons, transformed into dopamine, and stored in vesicles. Levodopa, therefore, increases dopamine available for release each time a dopaminergic neuron fires. Risperidone interferes with dopaminergic neurotransmission by binding to and blocking D_2-like dopamine receptors, which ultimately reduces the transmission of dopaminergic signals to postsynaptic neurons.[37]

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 intervention. 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 and risperidone. 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. Drug doses were decided on the basis of these ethical concerns and the binding request on the part of our local Institutional Review Board.

After completing a music reward task (described in Ref. 8), participants completed the musical memory task, which lasted approximately 45 min, followed by a language learning task (described in Ref. 32) and a monetary incentive delay task. The

Figure 1. **Schematic representation of the pharmacological intervention and the music memory paradigm.**

music reward and word learning tasks performed by the same cohort of participants differed from the one described in this study at both the theoretical and methodological (e.g., instructions and material) level (participants in one just listen to music without encoding; in the other, they learn new words from written context without any feedback). Participants started the current study (i.e., the music memory task) 1 h and 20 min after drug administration. Levodopa and risperidone usually reach maximal concentrations 1 h and 1–2 h after administration, respectively.[38,39] Therefore, participants performed all the tasks under the effect of the medications.

After the experimental session, participants spent their time in a resting room and were allowed to leave the hospital 6 h after the treatment administration. For each intervention, each participant came back 24 h later for a behavioral memory retesting (without any pharmacological intervention), which lasted about 15 minutes. At least 1 week passed between one intervention and the other.

The musical memory task employed has been validated and described in our previous work[25] (Fig. 1). In each intervention, participants were exposed three times to unfamiliar instrumental classical excerpts (normalized at −10 dB, and faded 3 s in and 3 s out). During the first exposure, volunteers listened through earphones to 24 excerpts, lasting 20 s each.[40] Participants were told to listen to the excerpts attentively, as they would be asked to remember them later. After each excerpt, they were asked to rate (on a 1- to 5-point scale) the general pleasantness (from 1 = no pleasure to 5 = intense pleasure) experienced when listening to the piece (i.e., "liking" reward measure[41]). Furthermore, in order to take into account important features likely to modulate the affective response to music as well as musical memory (see, e.g., Ref. 42), participants were asked to rate the level of arousal (from 1 = very relaxing to 5 = very arousing), emotional valence (from 1 = very sad to 5 = very happy), and familiarity (from 1 = completely unfamiliar to 5 = very familiar). Also, we asked participants to indicate in which position of a top-ten classification (i.e., "wanting" reward measure[41]), they would like to place each excerpt, knowing that the excerpts ranked in the first three positions were more likely to be part of a final Spotify playlist that they were going to receive by e-mail for their participation. The ratings, together with the rating scales, were visually presented one by one on a screen. The answers to each rating were self-paced. During the second exposure, participants were simply asked to listen again to the same excerpts, in order to be completely absorbed in music listening and encoding.[25] During the third exposure, they were asked to listen to them another time and to rate again general pleasantness and top-ten. The means of pleasantness and top-ten subjective ratings between the first and third exposure were computed and employed for the analyses further reported in Ref. 25, but see Figure S3 (online only for additional analyses of the pleasure ratings over the different exposures). One minute passed between each exposure to all 24 musical excerpts.

Twenty-four hours after learning, participants were presented with 24 old and 24 new excerpts lasting 10 s each. The selection of these 10-s pieces[43] was made by excluding the first and last 3 s (i.e., the faded ones) of the excerpts and by selecting at least one musical phrase. For each one, participants had to indicate if they had listened to it the

day before (old/new recognition). If they thought they had, they needed to commit to one of three additional options (recollection task): remember (R), know (K), or guess (G). R indicated that they could recollect something specific about the study episode; K indicated that they were confident that the excerpt was familiar, but they had no recollection; G responses were given when they were unsure about whether the excerpt was really heard the day before (R/K paradigm[31]).

In total, six lists of excerpts (balanced for emotional valence, arousal, general pleasure, and familiarity) were presented to each participant: three lists (one for each intervention) during the encoding session (i.e., old) and three during the test session, 24 h later (i.e., new). The order of the lists was counterbalanced across interventions. The six lists were created (pretested on $n = 60$ participants, 44 females, mean age $= 28.00 \pm 12.08$ years) so that there were no differences (one-way ANOVA and Bayes factors calculated with JASP 0.13.1.0) in arousal ($F(5,115) = 0.061$; $P = 0.997$; $\eta^2 = 0.003$; $BF_{10} = 0.019$), emotional valence ($F(5,115) = 0.193$; $P = 0.965$; $\eta^2 = 0.008$; $BF_{10} = 0.024$), general pleasure ($F(5,115) = 0.325$; $P = 0.897$; $\eta^2 = 0.014$), and familiarity ($F(5,115) = 0.371$; $P = 0.868$; $\eta^2 = 0.016$; $BF_{10} = 0.033$). In order to avoid any confounding effect due to familiarity, only items that were judged by participants as completely unfamiliar (rating $= 1$) were included in the analyses reported here. The total duration of this retrieval phase lasted about 20 minutes. Auditory stimuli were presented using a headset, and the overall loudness of the excerpts was adjusted subjectively to ensure constant loudness throughout the experiment.

Statistical analysis

Discriminability (d′) and response bias (c) indexes were computed to assess general memory performance and compared across conditions through repeated-measures ANOVA. We first tested whether participants' performance under the placebo condition replicated our previous results assessing musical memory and its relation to reward-related subjective ratings.[25] For each subject, we computed the average pleasantness ratings (provided during encoding) for musical excerpts that were later remembered (R), known (K), guessed (G), or forgotten. With the aim of comparing recollective to nonrecollective aspects of episodic memory, we then compared the differences between R/K/G responses (for correctly recognized items only) and forgotten items running repeated-measures ANOVA with a four-level within-subjects factor (pleasantness ratings for forgotten items, R, K, and G responses). Repeated-measures ANOVA was used here to be consistent with the reporting of previous studies using the same paradigm.[25] The same procedure was applied for the other subjective ratings (*arousal, emotional valence,* and *top-ten ratings)*. Note that from the final sample of 21 participants, only 17 had trials in all four conditions (three participants provided no G responses, and one participant provided no K responses), and thus ANOVA for the placebo condition was calculated with a sample of 17 participants.

While repeated-measures ANOVA was used to assess the relationship between musical memory and pleasure in the placebo condition for consistency with past research, to study the effect of the pharmacological intervention, we turned to linear mixed modeling. Given the strong variability among participants' responses during placebo, using linear mixed modeling allowed us to avoid using average values for conditions, and also ensured that (unlike with repeated-measures ANOVA) we did not lose participants from our final sample. In addition, we had strong theoretical *a priori* bases to hypothesize that musical hedonia would modulate the dopamine–memory relationship, and linear mixed modeling allowed us to include the BMRQ scores into a model in an elegant manner (e.g., we avoided creating two groups of participants separated into high and low musical hedonics using a median split). Thus, in order to test the implications of drug-induced dopaminergic modulation, musical reward sensitivity, and subjective pleasure experience on memory, we performed generalized linear mixed modeling in *R* (version 4.0.2) and *RStudio* (version 1.3.959) using the *lme4* package.[44] For both recognition and recollection performance, the dependent variable was assumed to have a binomial distribution and a logit link function was applied. For recognition, the dependent variable was whether each old excerpt was correctly recognized or not (i.e., forgotten); for recollection, the dependent variable was whether each old, correctly recognized excerpt was categorized as remembered or not (i.e.,

including all known, guessed, and forgotten excerpts). For the predictors, we first generated a minimal model based on well-validated theories regarding dopamine, reward, and memory and our own prior data. Specifically, on the basis of the results of our previous studies assessing the relationship between musical reward and memory[25] and the effects of a dopaminergic pharmacological intervention on the reward–memory effect[32] (note that in both studies reward sensitivity modulated the effect that reward had on memory), we included a triple interaction between drug (i.e., pharmacological session), musical reward sensitivity, and subjective pleasure ratings. On the basis of results obtained for the placebo session (which show a significant effect of arousal on memory; see Results), and as a further control, we also included subjective arousal ratings. In order to take into account possible effects of body weight on the drug dose,[28] we included participants' weight as a main fixed effect. Finally, because of the repeated nature of the study and in order to account for possible effects of practice and familiarity with the task, we included the order of the sessions as a main fixed effect. This led to the following model: *pleasantness∗drug∗BMRQ score + arousal + weight + order*.

We then generated different models adding further variables (i.e., *gender, age, emotional valence,* and *top-ten subjective ratings*) and interactions (*arousal∗drug, arousal∗BMRQ score,* and *arousal∗drug∗BMRQ score*) that could also play a role in predicting memory performance. All models included random intercepts for participants. Akaike information criterion (AIC) was used to select the model with the best balance between goodness of fit and complexity. Then, the effects of the different predictors and their interactions on memory performance were assessed by means of likelihood ratio tests (LRT) using the *afex* package in *R*. These tests were based on type 3 sums of squares. Following a significant interaction, pairwise post-hoc comparisons with Tukey's correction for multiple comparisons were used to test how the effects of musical reward sensitivity and subjective ratings on memory performance varied across pharmacological interventions. Contrasts were carried out using the *emmeans* package in *R*.[45]

An additional post-hoc power analysis for our main results (i.e., a triple interaction between musical pleasure, sensitivity to musical reward, and dopaminergic intervention; see Results) was run via the *simr* package,[46] using the powerSim function with 1000 simulations.

Results

Overall, participants performed well in the memory task, as shown by d′ and c rates for each session (group average per session with SD, for d′ and c, respectively: risperidone = 1.41 ± 0.85, 0.07 ± 0.30; placebo = 1.40 ± 0.78, 0.02 ± 0.27; levodopa = 1.44 ± 0.6; -0.05 ± 0.26). No significant differences between these indexes were found across pharmacological sessions (P's > 0.269).

First, we examined the placebo session in order to explore the relationship between pleasure and memory without pharmacological manipulation. Repeated-measures ANOVA during the placebo session revealed a main effect of pleasantness ratings according to memory responses ($F(3,48) = 4.683$, $P = 0.006$, $\eta^2 = 0.226$), with remembered excerpts rated as significantly more pleasant than forgotten ones ($t(48) = 3.081$, $P = 0.02$, Bonferroni-corrected, Fig. 2A). The analysis further revealed a general effect of for arousal ratings ($F(3,48) = 8.448$, $P < 0.001$, $\eta^2 = 0.346$), with remembered excerpts rated as significantly more arousing than guessed and forgotten ones ($t(48) = 3.070$, $P = 0.021$ and $t(48) = 3.498$ $P = 0.006$, respectively, Bonferroni-corrected, Fig. 2B). No significant differences were found for the other subjective ratings, namely, emotional valence and top-ten ratings (P's > 0.118). These findings are consistent with previous studies showing a link between pleasure and memory formation.[25,47]

Next, using linear mixed modeling (see the Methods section), we investigated to what extent this relationship was modulated by drug treatment and individual differences in musical reward sensitivity (i.e., we assessed the effect of the drug intervention). The generalized linear mixed models analysis for the recognition performance found five models as equally best candidates to explain the variance of the model (i.e., ΔAIC < 2 among them; 2 units of AIC is the limit to indicate that there is substantial evidence to support a candidate model, as a general rule of thumb): the minimal model (i.e., *pleasantness∗drug∗BMRQ score + arousal + weight + order*), the model including *emotional valence*, the model including *gender*, the model including an interaction between *arousal* and *drug*, and the

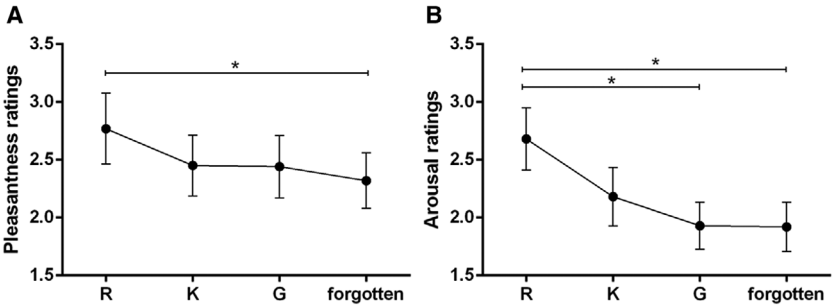

Figure 2. **Means and SEM of pleasantness (A) and arousal (B) ratings for general memory performance and familiarity-recollection processes (R, K, and G responses for correctly recognized items and forgotten items) obtained in the placebo session. ∗ indicates significant values ($P < 0.05$) from Bonferroni-corrected post-hoc pairwise comparisons.**

model including an interaction between *arousal* and *BMRQ score* (Table S1, online only). Even if there were five models separated by less than two AIC, we used the Akaike weight, which indicates the probability that the candidate model is the best among the set of candidate models, to select the final model for this analysis: *pleasantness∗drug∗BMRQ score + arousal + emotional valence + weight + order*. An in-depth analysis of this model using LRTs showed a significant main effect of *arousal* ($x^2(1) = 12.66$, $P < 0.001$; Table S2, online only), suggesting better recognition for the more arousing excerpts, regardless of the drug taken or the level of musical hedonia. In addition, results revealed a significant main effect of *order* ($x^2(2) = 11.38$, $P = 0.003$; Table S2, online only). Post-hoc comparisons showed that recollection performance was significantly greater in the first session than in the third one (Z ratio = 3.35, $P = 0.002$), thus ruling out the possibility that participants improved across sessions due to practice and familiarity with the study procedure.

Concerning the *recollection* performance, the model including the interaction between *arousal* and *drug* (i.e., *pleasantness∗drug∗BMRQ score + arousal∗drug + weight + order*) had considerably more support than the others ($w(AIC_c) = 0.71$, Table 1), and was therefore selected for subsequent analysis using LRTs. Crucially, and in line with our hypothesis, the results revealed a significant triple interaction among *pleasantness*, *drug* and *BMRQ score* ($x^2(2) = 6.14$, $P = 0.047$; Table 2), indicating that the memory recollection was modulated by an interplay between the pharmacological session (i.e., dopaminergic signaling), the subjective pleasure elicited by a particular song, and the participant's level of sensitivity to musical reward (i.e., musical hedonia). Post-hoc comparisons showed that the influence of subjective pleasure on recollection performance was modulated by risperidone, but that the modulation depended on subjects' sensitivity to reward (Z ratio = 2.44, $P = 0.015$). In other words, for participants with mid-to-low sensitivity to musical reward, when dopaminergic signaling was disrupted, the probability of remembering the musical excerpts did not increase depending on the pleasure experienced during the encoding of those songs. On the contrary, for participants with high levels of musical hedonia, the effect of pleasure on memory was present even when dopaminergic availability was lowered (Fig. 3).

These results suggest that a downregulation of dopaminergic transmission hinders the pleasure-driven effect on memory, specifically in participants with medium to low music reward sensitivity. The results also showed a significant interaction between *drug* and *pleasantness* ($x^2(2) = 6.65$, $P = 0.036$). However, since this double interaction is part of a model in which there is a significant triple interaction, it should be interpreted with caution and it will not be further discussed. In sum, these findings show that the relationship between musical pleasure and memory, confirmed by the analysis on the placebo session, is modulated by dopaminergic transmission, and that this effect also depends on participants' sensitivity to musical reward (i.e., musical hedonia).

The results also revealed a significant interaction between *arousal* and *drug* ($x^2(2) = 9.80$, $P = 0.007$; Table 2). Post-hoc comparisons showed

Table 1. Model selection for recollection

Model	K_i	AIC_{ci}	$\Delta_i(AIC_c)$	$w_i(AIC_c)$	$\log(L_i)$
Pleas∗drug∗BMRQ + arousal∗drug + weight + order	19	1448.5	0.00	0.71	−704.9
Pleas∗drug∗BMRQ + arousal∗drug∗BMRQ + weight + order	22	1451.6	3.14	0.15	−703.4
Pleas∗drug∗BMRQ + arousal + weight + order	17	1454.1	5.69	0.04	−709.8
Pleas∗drug∗BMRQ + arousal∗BMRQ + weight + order	18	1454.9	6.39	0.03	−709.2
Pleas∗drug∗BMRQ + arousal + weight + order + gender	18	1455.8	7.33	0.02	−709.6
Pleas∗drug∗BMRQ + arousal + weight + order + top-ten	18	1455.9	7.47	0.02	−709.7
Pleas∗drug∗BMRQ + arousal + weight + order + age	18	1456.1	7.64	0.02	−709.8
Pleas∗drug∗BMRQ + arousal + weight + order + EmVa	18	1456.2	7.71	0.02	−709.8
null	2	1522.7	74.3	0.00	−759.4

NOTE. Candidate models for recollection. All models included random intercepts for participants. In the formulas, Pleas = pleasantness, BMRQ = BMRQ score, EmVa = emotional valence. ∗ indicates an interaction. K_i = the number of estimated parameters for model *i*. AIC_{ci} = corrected Akaike information criterion. $\Delta_i(AIC_c)$ = difference between AIC_c for model *i* and best model's AIC_c. $w_i(AIC_c)$ = the Akaike weight measuring the level of support in favor of model *i* being the most parsimonious among the candidate model set. $\log(L_i)$ = natural logarithm of the maximum likelihood for model *i*.

that the influence of subjective arousal on recollection performance was significantly larger after placebo intake than after risperidone and levodopa intake (Z ratio = 2.54, $P = 0.030$; and Z ratio = 2.83, $P = 0.013$, respectively; Fig. S1, online only), suggesting that the pharmacological intervention indiscriminately hindered the effect of arousal on memory. A main effect of *arousal* ($x^2(1) = 42.7$, $P < 0.001$) was also found, but its interpretation is limited by the significant double interaction that also includes *arousal*. Finally, the results revealed a significant main effect of *order* ($x^2(2) = 13.01$, $P = 0.001$). Post-hoc comparisons showed that recollection performance was significantly greater in the first session than in the third one (Z ratio = 3.59, $P = 0.001$; Fig. S2, online only).

The post-hoc power analysis for our main result in the Recollection model showed that the power to find a significant triple interaction as compared with one with only main effects of musical pleasure, sensitivity to musical reward, and dopaminergic intervention was 96% (95% confidence interval: 86.29–99.51%). This proves that our results are sufficiently powered.

Discussion

Our findings show that dopaminergic synaptic availability, when manipulated through a within-subject, double-blind pharmacological paradigm, modulates the pleasure-driven episodic memory for one the most iconic abstract rewards in humans: music. More specifically, we found that the disruption of dopaminergic transmission through risperidone decreases the probability that a highly pleasurable excerpt will be remembered after a 24-h consolidation period. Furthermore, our findings show that the memory effects induced by the pharmacological intervention modulated participants' performance depending on their sensitivity to musical reward (i.e., musical hedonia).

A main finding of the present study concerns the dopamine-dependent, reward-potentiated effect on music memory, supporting previous research showing that rewarding stimuli enhance memory formation via dopaminergic pathways.[17,19,22,48,49] Dopamine-dependent protein synthesis in the hippocampus would promote long-term memory consolidation processes, thus leading to better episodic memory performance.[17] Accordingly, we found that dopaminergic transmission mainly plays a role in regulating recollection.[28]

Our findings point to a main role of dopamine disruption (i.e., via risperidone) rather than of dopamine enhancement (i.e., via levodopa) on episodic memory. On the one hand, this crucially underlines that dopamine release is a necessary condition for long-term memory processes to take place.[50] On the other hand, this seems in contrast with previous pharmacological interventions showing that increasing the synaptic availability of dopamine enhances learning and memory.[28,30,34,51] Note, however, that the purpose of this study was to elucidate whether the modulation of the dopaminergic system influenced the variable under study

Table 2. Type III ANOVA on likelihood ratio tests for recollection performance

Predictor	Df	x^2	Df(x^2)	*P*
Intercept	16	0.15	1	0.695
Drug	15	7.09	2	**0.029***
BMRQ score	16	2.52	1	0.112
Pleasantness	16	1.39	1	0.238
Arousal	16	41.9	1	**<0.001*****
Weight	16	0.12	1	0.731
Drug∗BMRQ score	15	6.56	2	**0.038***
Pleasantness∗drug	15	6.71	2	**0.035***
Pleasantness∗BMRQ score	16	1.99	1	0.159
Arousal∗drug	15	10.3	2	**0.006****
Pleasantness∗drug∗BMRQ score	15	6.01	2	**0.049***

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. df, degrees of freedom.

(i.e., the relationship between reward and memory), rather than to assess the capacity of the drugs themselves to block or enhance the natural physiological responses influenced by dopamine. Indeed, other studies assessing the influence of levodopa only (i.e., not using an antagonist, such as risperidone) on episodic memory have reported a dose-dependent nonlinear effect with higher doses of medication than the ones used in this work (i.e., 150 mg in the case of Ref. 28). Therefore, it is possible that the dose amount chosen for this study (i.e., 100 mg) is not enough to drive a specific effect on episodic memory by itself. Also, the interpretation of our findings should be done bearing in mind the small sample size, even if the main results are sufficiently powered (see the post-hoc power analysis in the Results section). Furthermore, our results do not exclude an effect of dopamine precursor (i.e., levodopa) on memory performance but rather suggest that (1) dopaminergic disruption (i.e., via risperidone) mainly modulates the memory performance specifically driven by musical pleasure and (2) the effect of pharmacological intervention on memory depends on interindividual differences in musical hedonia.

Our results are in line with previous research indicating a tight link between dopamine and musical pleasure. Key dopaminergic regions, such as the ventral striatum (VS) and the midbrain, respond to highly pleasurable musical stimuli.[1,4,5] We recently showed, via pharmacological intervention, a causal role for dopaminergic transmission in the hedonic reaction to music.[8] Here, by showing a dopaminergic-driven modulation of the effect of pleasure on memory, we suggest that such dopamine-dependent musical pleasure is also crucial for successful episodic memory. One possible interpretation of this finding relies on reward prediction mechanisms, which are known to increase dopaminergic release.[52,53] Abstract rewards, such as music, are strongly dependent upon perceptual expectations and predictions.[54] Both theoretical considerations and experimental findings suggest that music represents a learning challenge by itself—triggered by the presence and violation of musical regularities—and that reward-related activations induced by music may be driven by the intrinsic value of successfully anticipating potential musical surprises.[6] In the context of prediction, data posit that dopaminergic neurons in the VS (and the nucleus accumbens) are the key factor driving the attachment of hedonic value to music[5,55] (but see also Ref. 56). Importantly, reward prediction errors (RPEs) are also crucial for reinforcement learning processes and episodic memory.[57–59] It is, therefore, possible that the dopamine-dependent RPEs underpinning musical pleasure during encoding might also promote episodic memory formation for the same material via the substantia nigra/ventrotegmental area-hippocampal loop.[57] Further investigation focused on musical RPEs is needed in order to confirm such an interpretation.

The current findings draw a complex picture of the relationship between abstract rewards and human memory (see also Ref. 32): interindividual differences in music reward sensitivity appear to play a crucial role in musical memory formation and also in modulating the intense pleasure that music can evoke.[11] Previous studies suggested that dopaminergic stimulation may improve cognitive performance in subjects with lower baseline cognitive abilities while worsening it in those with higher baseline abilities.[60–62] These differences at baseline, particularly in memory-related tasks, may reflect individual differences in dopaminergic transmission,[63–65] and indicate an inverted U-shaped relationship between cognition and dopamine: maximal cognitive performance exists at an optimal dopamine level, above or below which the performance worsens.[65] Notably, and in line with this literature, our findings suggest that the

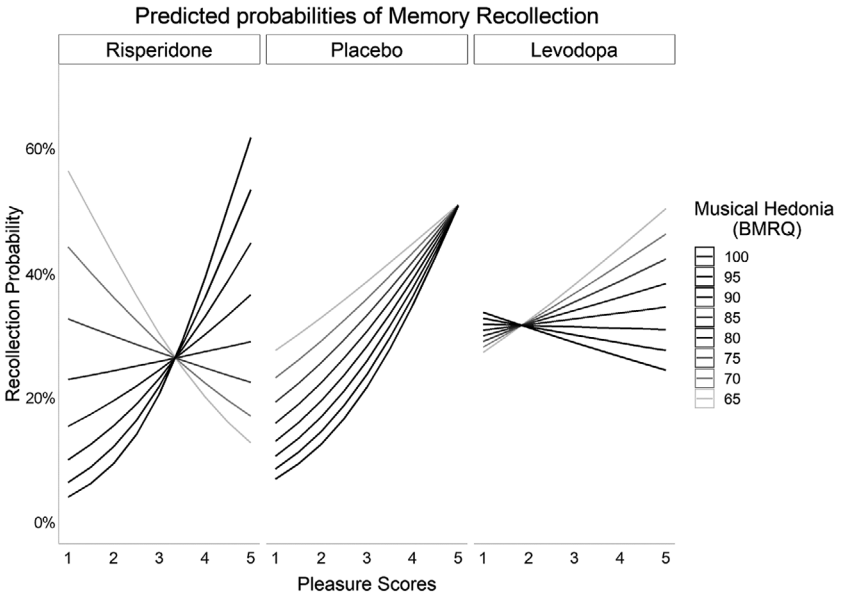

Figure 3. **Partial effects computed from the parameters of the linear mixed model *drug∗BMRQ score∗pleasantness + arousal∗drug + weight + order*, and representing the estimated probability of memory recollection as a function of pleasure ratings, drug, and individual differences in musical hedonia (BMRQ). For the latter, predicted slopes are shown for individuals with low (lighter gray) to high (darker gray) sensitivity to musical reward (the higher the BMRQ value, the higher the music reward sensitivity; each line represents the prediction for a hypothetical individual with a specific BMRQ score). Risperidone and levodopa differentially modulate the relationship between pleasure and memory, according to different musical hedonia scores. As highlighted by post-hoc analysis, the significant difference across subjects is driven by the risperidone intervention. This plot was generated using the ggpredict function from the *ggeffects* package in *R*.**

drug manipulation differentially modulated participants' performance as a function of their sensitivity to musical reward. Under levodopa, there is a trend toward greater reward-potentiated effects on music in individuals with lower music reward sensitivity, who generally show poorer reward–memory effects[25,47] and reduced engagement of dopaminergic circuits while listening to music.[14] Thus, only individuals with low sensitivity to music benefited from the increase in dopaminergic transmission, while performance in music hedonic individuals was disrupted. Under risperidone, individuals with high music hedonia showed the strongest reward-potentiated effects on memory. Thus, lowering dopaminergic transmission disrupted the relationship between reward and memory in individuals with low sensitivity to music, while leaving unaffected the performance of high hedonic individuals. The fact that drug effects on memory and reward depended on individuals' music reward sensitivity further supports that reward-potentiated effects on music memory may rely on dopaminergic transmission. Note that medium and lower hedonic participants in this study scored within the normal values of the BMRQ. Further investigation, including also musical anhedonics, who usually do not experience musical pleasure at placebo, would be needed to better disentangle such complex interplay.

However, it is noteworthy that the relationship between reward and memory was not only disrupted, but reversed in low-musical hedonic individuals, who showed a better memory for unpleasant than pleasant music (Fig. 3). At a behavioral level, this could suggest that when the mechanism subserving reward-driven memory was impaired, participants with low sensitivity to musical reward relied on different encoding strategies that in turn benefitted the nonpleasant experimental condition. At a neural level, one possible interpretation relies on previous studies highlighting that dopaminergic levels may modulate the balance between reward (approach) and punishment (avoidance) sensitivity through regulation of Go (via D_1 receptors) and No-Go (via D_2 receptors) pathways, respectively.

Increases in dopamine bias participants toward positive outcomes, whereas dopamine depletion has the opposite effect, supporting the avoidance of negative outcomes.[66,67] Therefore, it is possible that for individuals with lower musical hedonia, the risperidone-driven dopamine reduction in the striatum might have led to a better memory performance even in unpleasant music via No-Go pathways.

Although we also found an effect of musical arousal on memory, it is unlikely that such memory facilitation relies on the same dopaminergic-dependent reward mechanisms as it does for pleasure. Indeed, the arousal effect was indiscriminately found during recognition and recollection, and it was hindered by both risperidone and levodopa, without interacting with participants' musical hedonia. This would, therefore, suggest a reward-independent, nonspecific effect of pharmacological intervention on perceived arousal, which is ultimately able to modulate the memory performance.

Taken together, these findings indicate new avenues for the study of the underlying mechanisms of music-driven memory benefits[24] and their implications in the clinical domain[68–70] (see Ref. 71 for a review). By showing that musical reward is a crucial mechanism in music memory performance, our results suggest that interindividual differences in musical hedonia should be taken into account in memory stimulation and rehabilitation paradigms (see also Refs. 72 and 73). Such broadened paradigms could promote more finely grained musical interventions in normal and pathological aging, for example.[74] To that end, the current findings may represent an important first step in novel investigations of pathological aging since musical memory constitutes a special type of memory often spared in disorders like Alzheimer's disease.[75]

In conclusion, we show that pharmacologically manipulating dopaminergic signaling modulates the effect of pleasure on long-term recognition memory for musical pieces, but that this happens differently according to the subject's sensitivity to musical reward. By employing music as an ideal tool for the study of reward processes, this work emphasizes the versatility of the human dopaminergic reward system: dopamine signaling lies at the core of the memory benefits mediated not only by explicit or primary rewards but also by abstract and aesthetic rewards, such as music.

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Author contributions

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

Supporting information

Additional supporting information may be found in the online version of this article.

Table S1. Model selection for recognition.

Table S2. Type III ANOVA on likelihood ratio tests for recognition performance.

Figure S1. Partial effects (with 95% confidence intervals) computed from the parameters of the

linear mixed model *drug∗BMRQ score∗pleasantness + arousal∗drug + weight + order*.

Figure S2. Order effect (with 95% confidence intervals) computed from the parameters of the linear mixed model *drug∗BMRQ score∗pleasantness + arousal∗drug + weight + order*.

Supplementary analyses on pleasure ratings.

Figure S3. Subjective pleasure ratings provided during the first and third exposure to unfamiliar classical music excerpts under risperidone, placebo, and levodopa.

Competing interests

The authors declare no competing interests.

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