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Archival Report

Dopaminergic D_1 Receptor Stimulation Affects Effort and Risk Preferences

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ABSTRACT

BACKGROUND: Activation of D_1 receptors has been related to successful goal-directed behavior, but it remains unclear whether D_1 receptor activation causally tips the balance of weighing costs and benefits in humans. Here, we tested the impact of pharmacologically stimulated D_1 receptors on sensitivity to risk, delay, and effort costs in economic choice and investigated whether D_1 receptor stimulation would bias preferences toward options with increased costs in a cost-specific manner.

METHODS: In a randomized, double-blind, placebo-controlled, parallel-group phase 1 study, 120 healthy young volunteers received either placebo or 1 of 3 doses (6 mg, 15 mg, or 30 mg) of a novel, selective D_1 agonist (PF-06412562). After drug administration, participants performed decision tasks measuring their preferences for risky, delayed, and effortful outcomes.

RESULTS: Higher doses of the D_1 agonist increased the willingness to exert physical effort for reward as well as reduced the preference for risky outcomes. We observed no effects on preferences for delayed rewards.

CONCLUSIONS: The current results provide evidence that D_1 receptor stimulation causally affects core aspects of cost-benefit decision making in humans.

Keywords: D_1 receptors, Decision making, Dopamine, Effort discounting, Risk, Temporal discounting

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Economic choice often requires assessing and trading off benefits (rewards) and costs (1). Costs in economic choice come in various forms, including physical exertion required to obtain a benefit (effort), uncertainty in benefit delivery (risk), or waiting time for benefit delivery (delay). These costs lower the subjective value of benefits, reducing the propensity of pursuing high-benefit, high-cost goals. Deficits in cost-benefit decision making belong to the core symptoms of several psychiatric disorders, including schizophrenia, addiction, or depression (2). It is thus important to understand neuropharmacological mechanisms that are causally involved in cost-benefit computations.

The neurotransmitter dopamine, which acts on D_1 receptor (D_1R) and D_2 receptor (D_2R) families, has been ascribed a central role in integrating costs and benefits. Receptors of the D_1 family reside predominantly in the direct go pathway, which links the striatum with the output regions of the basal ganglia and plays a crucial role in encoding reward outcomes (3). Moreover, D_1Rs are also more prevalent than D_2Rs in regions outside the basal ganglia, particularly prefrontal cortex (4). Stimulation of prefrontal D_1Rs was linked to enhanced goal representations in working memory and lower susceptibility to distracting information (5–7). In contrast, a prefrontal D_2-dominated state was associated with more flexible, but also less goal-directed, behavior. Both D_1R activation in the striatal direct pathway and activation in the prefrontal cortex might increase reward sensitivity and thus improve the willingness to tolerate costs to achieve one's goals. This is because a frontostriatal network is hypothesized to perform domain-general cost-benefit computations (8). In contrast, the finding of cost-specific neural mechanisms (1) would predict cost-specific effects of D_1R activation. We therefore tested whether D_1R over D_2R activity differentially diminishes the subjective costs of 1) risk, 2) time, and 3) effort in human decision making.

Until recently, it had not been possible to achieve selective and prolonged stimulation of D_1Rs in the human brain. Accordingly, dopaminergic involvement in human cost-benefit weighting has primarily been shown for D_2Rs, with higher or lower D_2R activity increasing or reducing, respectively, subjective delay (9–12), risk (13–15), and effort (16) costs. Evidence in animal studies is mixed, as some studies related D_1 activation to lower sensitivity to economic costs (17–20), while other studies reported higher sensitivity (21,22). Some of these inconsistencies might be explained by a nonlinear (e.g., inverted U-shaped) relationship between D_1 activation and cost-benefit decision making (23), such that the impact of dopaminergic manipulations critically depends on baseline dopamine levels (24). This account predicts that D_1R stimulation will increase willingness to tolerate costs in individuals with low baseline dopamine levels but decrease it in individuals with high baseline levels.

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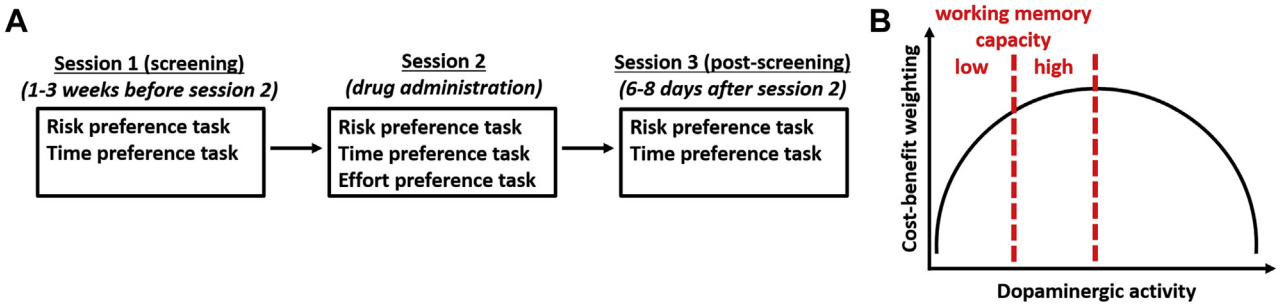

Figure 1. **(A)** Study overview. In a baseline screening session (session 1), volunteers were tested for study eligibility and performed baseline measures for risk and time preferences. In the main experimental session (session 2), participants received placebo or 1 of 3 doses of the D_1 agonist PF-06412562. Five hours after drug intake, they performed tasks that assessed risk, time, and effort preferences and thereby allowed us to measure the impact of the drug on the willingness to tolerate costs for larger benefits. Finally, in a postscreening session (session 3), participants were checked for potential side effects and performed tests for risk and time preferences. **(B)** The relationship between cost-benefit decision making and prefrontal dopaminergic activity is thought to follow a nonlinear (e.g., inverted U-shaped) function. The impact of the D_1 agonist on economic preferences might therefore depend on baseline differences in working memory capacity as proxy for dopamine synthesis capacity.

Here, we used PF-06412562, a novel selective dopamine D_1/D_5 receptor partial agonist (25–27), to investigate the causal involvement of D_1R stimulation in economic decision making (given that specific functions of D_1 and D_5 have not been elucidated yet, "D_1R" here refers to both D_1R and D_5R). Specifically, this study tested the hypothesis that pharmacologically increasing D_1R activity changes the willingness to tolerate risk, delay, and effort costs during cost-benefit decision making (Figure 1A). To assess the possibility that the impact of D_1R stimulation depends on baseline dopaminergic activity (due to a nonlinear relationship between D_1 activity and cost-benefit decision making) (Figure 1B), we tested whether the impact of D_1R stimulation on decision making depends on baseline differences in working memory capacity (WMC). WMC is thought to approximate baseline dopamine synthesis capacity (28,29).

METHODS AND MATERIALS

Participants

The study protocol was approved by the Research Ethics Committee of the canton of Zurich (2016-01693) and the Swiss agency for therapeutic products (2017DR1021). The study was carried out in accordance with the Declaration of Helsinki, amendment of Fortaleza, Brazil, 2013, and all pertinent guidelines and laws in force in Switzerland. The study was registered on ClinicalTrials.gov (NCT03181841). A total of 147 volunteers who were recruited at the University of Zurich were screened for this study. In a screening session, volunteers underwent a thorough medical examination to assess their eligibility for the study. All participants gave written informed consent before the start of the screening examination. From this pool of screened volunteers, 120 participants (59 female, mean age = 22.57 years, range 18–28) were invited to participate in the study. For their participation, participants received 480 Swiss francs and a monetary bonus depending on their choices (see below).

Study Design and Procedures

The current study was a monocentric, randomized, double-blind, placebo-controlled, and parallel-group clinical phase 1 trial. The 120 participants were randomly assigned to 1 of 4 experimental arms, 1 arm receiving placebo (lactose) and the other 3 arms a single dose (6 mg, 15 mg, or 30 mg) of the D_1 agonist PF-06412562 in modified release form (for preclinical specificity analyses, see the Supplemental Methods).

Participants completed 3 sessions (Figure 1A). In session 1 (duration = 1 hour), they were screened for potential exclusion criteria including history of psychiatric or other chronic disorders and abnormalities in vital signs, electrocardiogram, blood, and urine. All participants performed a urine drug test, and female participants additionally performed a pregnancy test. As baseline measures, participants filled in questionnaires measuring reward sensitivity [Behavioral Inhibition System/Behavioral Activation System scale (30)], verbal intelligence [Mehrfachwahl-Wortschatz-Intelligenztest B (31)], and impulsivity [Barratt Impulsiveness Scale-11 (32)]. In addition, participants' baseline time and risk preferences were measured (see below for details), as well as working memory performance using the digit span backward. The digit span backward represents a widely used measure for WMC (i.e., the maximum number of items that can be maintained and manipulated in working memory). For all of these baseline measures, we observed no significant group differences (Supplemental Results and Supplemental Table S3).

At the start of session 2 (7–21 days after session 1; duration = 9 hours), predose measures of vital signs and blood and urine samples were collected. Before substance intake, participants performed the digit span task backward. After the observed drug intake, participants stayed at the study site and were continuously monitored for potential side effects. Venous blood samples for the quantification of PF-06412562 and its metabolite PF-06663872 in plasma were withdrawn exactly 4 and 8 hours, respectively, after drug intake. Together with the 8-hour pharmacokinetics sample, postdose measures of vital signs, blood and urine values, and an electrocardiogram were also obtained. Five hours after drug intake (close to expected maximum plasma concentrations of the modified release form), participants performed in balanced, pseudorandom order a computerized battery of tasks measuring time preferences, risk preferences, effort preferences, reversal learning, Pavlovian-to-instrumental transfer, and exploration-exploitation

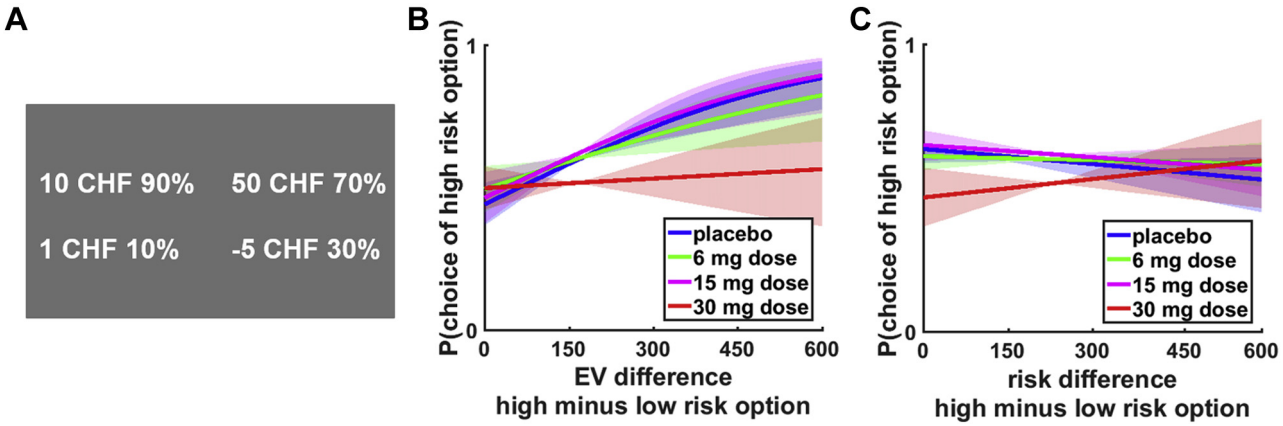

Figure 2. **(A)** In the risk preference task, participants made choices between 2 lotteries (e.g., 10 Swiss francs [CHF] with 90% or 1 Swiss franc with 10% vs. 50 Swiss francs with 70% or −5 Swiss francs with 30%). **(B, C)** Mean logistic curves indicating the probability (P) of choosing the riskier, higher expected value (EV) option as function of difference in **(B)** expected value and **(C)** risk between the options. Increasing doses of the D_1 agonist (particularly in the 30-mg group) reduced the preference for the high-risk option as the option difference **(B)** in expected value increased or **(C)** in risk decreased. Shaded areas indicate the 95% confidence interval.

decisions. The tasks were incentive compatible, and participants knew beforehand that at the end of the experiment, one trial of each task would be selected randomly, implemented, and the corresponding payoffs would be added to or subtracted from their payment. In this article, we report the results only of the 3 tasks measuring time, risk, and effort preferences; data on the other tasks (measuring reward learning rather than economic preferences) will be reported separately.

Finally, in session 3 (6–8 days after session 2; duration = 0.5 hours), participants were again screened for side effects and for potential drug effects on electrocardiographic measures as well as blood and urine samples. We again assessed WMC. Moreover, we asked whether time and risk preferences returned to baseline.

Behavioral Assessments

In the risk preference task, participants made choices between 2 compound lotteries (e.g., lottery 1: a gain of 10 Swiss francs with 90% and a gain of 1 Swiss franc with 10% chance; lottery 2: a gain of 50 Swiss francs with 70% and a loss of 5 Swiss francs with 30% chance) (Figure 2A). We used an adaptive task version [dynamic experiments for estimating preferences (33)] that allows estimating a participant's risk attitude (defined by the prospect theory parameters value curvature σ, probability distortion α, and loss aversion λ) with a relatively low number of trials (see the Supplement).

In the time preference task, participants made choices between smaller-sooner ([SS]; e.g., 10 Swiss francs today) and larger-later (e.g., 16 Swiss francs in 90 days) rewards (Figure 3A). In the task version applied in session 2, we administered all combinations of SS (0–16 Swiss francs today) and larger-later reward options (16 Swiss francs delivered after delays of 1–180 days) (34). For the baseline measures in sessions 1 and 3, a quicker, dynamic time preference task was used in a similar way as for the risk preference task (33) (see the Supplement).

In the effort preference task, participants could obtain a monetary bonus by exerting physical effort (squeezing a handgrip for 20 seconds with 40%–100% of their maximum grip force) (Figure 4A) (35). On each trial, participants made choices between effort-free (1 Swiss franc for 0% effort) and effortful (1.5–5 Swiss francs for 40%–100% effort) reward options (Figure 4B). To avoid fatigue and increase similarity of

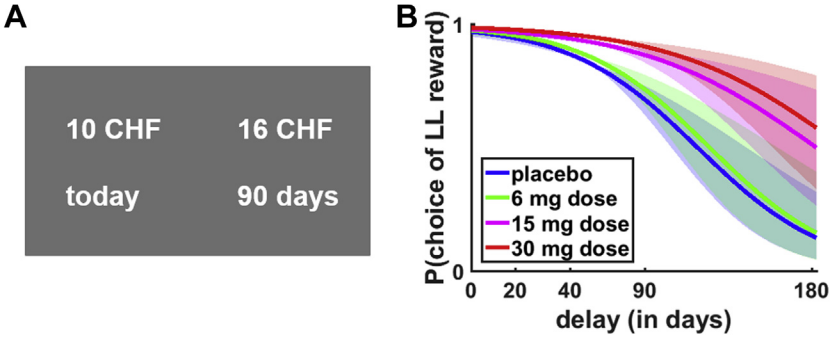

Figure 3. **(A)** In the time preference task, participants made choices between smaller-sooner (e.g., 10 Swiss francs [CHF] today) and larger-later ([LL]; e.g., 16 Swiss francs in 90 days) rewards. **(B)** We observed no significant drug effects on the impact of delay on time preferences. Shaded areas indicate the 95% confidence interval. P, probability.

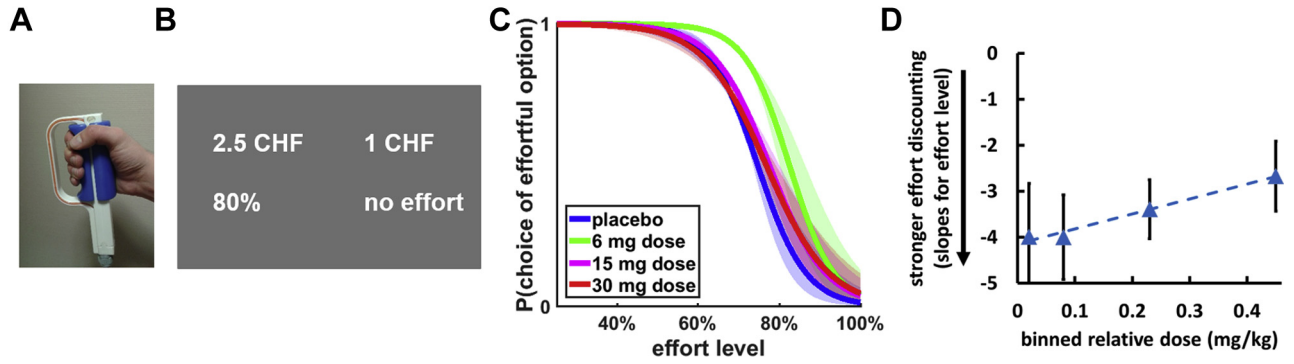

Figure 4. **(A)** In the effort preference task, we used a grip force dynamometer to vary effort requirements. **(B)** Participants chose between a smaller reward (1 Swiss franc [CHF]) requiring no effort and a larger reward (1.5–5 Swiss francs) requiring effort (squeezing with 40%–100% of their maximum force for 20 seconds). **(C)** Mean logistic curves indicating the probability (P) of choosing the effortful reward option as function of effort level. While effort discounting (indicated by the slopes of the logistic functions) was steepest in the placebo group, increasing doses of the D_1 agonist reduced the impact of effort on choices, indicating reduced effort discounting. We note, though, that the impact of the D_1 agonist on effort discounting was significant only for individualized measures of drug exposure, in other words, for relative dose **(D)** and plasma concentration, but not for absolute dose. Shaded areas and error bars indicate the 95% confidence interval.

implementation with the risk and time preference tasks, participants did not have to exert the effort immediately after having accepted an offer but only for a randomly selected choice at the end of the experimental session (see Supplemental Methods).

Data Analysis

The statistical analysis of the behavioral data was performed with MATLAB version R2016b (The MathWorks, Inc., Natick, MA) and IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY). For the model-free analyses of risk, time, and effort preferences, we used mixed generalized linear models as implemented in SPSS (for details, see Supplemental Methods). The alpha threshold was set to 5% (2-tailed) for all analyses.

To account for nonlinear (i.e., baseline-dependent) relationships between dopamine and decision making, we used WMC as proxy for baseline dopaminergic activity (28,36,37), because WMC was found to (linearly) relate to dopaminergic synthesis capacity (29). Samples were therefore split into a low WMC (median and below; i.e., 6 or less correct responses) and a high WMC group (above median; i.e., 7 or more correct responses) based on digit span backward performance in session 2. We used WMC as binary, rather than continuous, predictor because 23% of all participants reached the maximum performance level in the digit span task. Thus, a continuous measure of WMC would have misrepresented individual differences in high WMC. For 1 participant no digit span data were available for session 2. This participant was assigned to the low WMC group based on the session 1 digit span data. Using mixed generalized linear models, we modeled the linear effects of absolute dose (placebo, 6 mg, 15 mg, 30 mg), and WMC group for all analyses. Importantly, the absolute dose × WMC interaction assessed potential baseline-dependent effects of the D_1 agonist. In addition to modeling drug effects by absolute dose, all analyses were also conducted with relative dose (absolute dose divided by individual body weight in kilograms) and plasma concentration (mean of pharmacokinetic samples for PF-06412562 4 and 8 hours after drug administration) (Supplemental Table S2) as individualized measures of drug dose.

RESULTS

D_1R Stimulation Increases Risk Aversion

In the risk preference task (Figure 2A), we tested whether the D_1 agonist modulated the impact of expected value or risk on decisions under risk in the main experimental session. We regressed choices of the high-risk lottery (which was, by design, in most cases also the option with the higher expected value) on predictors for the WMC group, absolute dose, differences in expected value (EV_{diff}) and risk ($Risk_{diff}$) between the high- and low-risk lotteries, as well as the interactions between these factors. Increasing differences in expected value increased the probability of choosing the high-risk option ($\beta = 1.08$; $t_{7184} = 5.27$; $p < .001$), whereas increasing differences in risk reduced it ($\beta = -0.20$; $t_{7184} = 2.15$; $p = .03$) in line with value-seeking and risk-averse decision making.

With regard to drug effects, we observed a main effect of absolute dose ($\beta = -0.014$; $t_{7184} = 2.08$; $p = .04$), suggesting a lower preference for high-risk lotteries (more risk aversion) with increasing doses. This effect was specified by interactions with EV_{diff} ($\beta = -0.029$; $t_{7184} = 2.48$; $p = .01$) and $Risk_{diff}$ ($\beta = 0.011$; $t_{7184} = 2.01$; $p = .04$). As illustrated in Figure 2B, C, higher doses increased risk aversion particularly at higher expected value and lower risk differences between options. The mixed generalized linear model also yielded significant $EV_{diff} \times Risk_{diff}$ ($\beta = -0.57$; $t_{7184} = 3.86$; $p < .001$), as well as absolute dose × EV_{diff} × $Risk_{diff}$ interactions ($\beta = 0.020$; $t_{7184} = 2.44$; $p = .01$), further corroborating that D_1R stimulation reduced the willingness to take the riskier option, the larger the difference in expected value and the smaller the difference in risk between options. There was no evidence that drug effects were modulated by WMC (all $t_{7188} < 1$; all $p > .36$). We note that these results were robust to modeling drug effects as relative dose (all $t_{7188} > 3.06$; all $p < .002$) or plasma concentration (all $t_{7188} > 2.70$; all $p < .007$). Together, these findings suggest

that D_1 receptors causally contribute to determining subjective value during decisions under risk. In addition to the model-free findings, we performed a model-based analysis based on prospect theory parameters, which, however, revealed only nonsignificant trend-level effects of D_1R stimulation on risk and loss aversion (Supplemental Results).

No Evidence for Effects of D_1R Stimulation on Time Preferences

Next, we assessed whether the D_1 agonist affected the willingness to tolerate delay costs in intertemporal choice (Figure 3A). We analyzed intertemporal choices by regressing dummy-coded choices (delayed vs. immediate reward options) on predictors for WMC, absolute dose, delay, SS reward magnitude, and the interaction terms. As expected, the probability of choosing delayed rewards decreased with increasing delay ($\beta = -1.68$; $t_{6464} = 8.23$; $p < .001$), as well as with increasing amount of the SS reward option ($\beta = -3.59$; $t_{6464} = 15.48$; $p < .001$). Under placebo, participants were more patient in the high compared with the low WMC group ($\beta = 1.08$; $t_{6464} = 2.42$; $p = .02$). Importantly, however, this analysis revealed no significant main or interaction effects with the factor absolute dose (all $t_{6464} < 1.13$; all $p > .14$) (Figure 3B, C). Again, this null result also held when we replaced absolute dose by relative dose (all $t_{6464} < 1.29$; $p > .19$) or plasma concentration (all $t_{6464} < 1.36$; all $p > .17$). A model-based analysis of time preferences also yielded no significant drug effects (see Supplemental Results). Thus, contrary to our prediction, no significant effects of D_1R stimulation were observed on time preferences.

D_1R Stimulation Enhances Willingness to Engage in Rewarded Effort

Finally, we tested whether D_1R stimulation causally contributes to tolerating effort costs for rewards in the effort preference task (Figure 4A, B). We regressed dummy-coded choices of the effortful reward option on predictors for absolute dose, effort, reward magnitude, WMC, and the interactions between these factors. The resulting significant effects of effort ($\beta = -3.73$; $t_{9584} = 10.71$; $p < .001$) and of reward magnitude ($\beta = 2.23$; $t_{9584} = 7.94$; $p < .001$) indicate that the preference for the effortful reward option decreased with increasing effort requirements and decreasing reward magnitudes on offer. The impact of absolute dose on choice did not interact with effort level or reward magnitude (all $t_{9584} < 1.34$; all $p > .18$). Importantly, however, when drug effects were modeled as relative dose or plasma concentration (which capture individual drug exposure more realistically than absolute dose does), the impact of effort level on choices interacted with both relative dose ($\beta = 2.63$; $t_{9584} = 1.97$; $p = .041$) and plasma concentration ($\beta = 0.05$; $t_{9584} = 1.97$; $p = .049$) (Figure 4C, D). These findings suggest that effort discounting was weaker as the individualized concentrations of the D_1 agonist increased. No significant interactions were observed between drug effects and WMC or reward magnitude (all $t_{9584} < 1.58$; all $p > .11$). These model-free findings were corroborated by a model-based analysis showing that higher D_1 agonist doses reduced effort discounting using the best-fitting linear discount model. Specifically, the model-based analysis revealed significant drug effects on effort discounting for both absolute and relative doses, while the impact of plasma concentration was marginally significant (Supplemental Results). In sum, these results are consistent with the hypothesis that D_1R activation reduces the discounting of subjective reward value with increasing effort costs.

DISCUSSION

To elucidate the role of D_1Rs for human economic decision making, our study used a novel, selective agonist. We find (to the best of our knowledge, for the first time) that pharmacologically increasing D_1R activation modulates the sensitivity to risk and effort costs in human economic choice.

For effort costs, increasing D_1 agonist doses reduced the discounting of monetary rewards with increasing effort when employing individualized measures of drug exposure (relative dose and plasma concentration). This finding is in line with animal studies relating D_1 activation to enhanced willingness to exert physical effort for rewards (20,38,39). Anatomically, the motivation to engage in rewarded effort is associated with activation in dopaminoceptive regions such as the striatum and anterior cingulate cortex (40–43). The D_1 agonist might have reduced effort discounting by influencing activation involved in trading off rewards against the required effort costs. The effect was not modulated by individual differences in baseline WMC, in line with a robust relation between D_1R activation and motivation.

With regard to risk preferences, increasing D_1 agonist doses lowered preferences for riskier lotteries with higher expected values, suggesting increased risk aversion under strong D_1R activation. Also the analysis of prospect theory parameters revealed weak, trend-level effects of D_1R stimulation on risk (and loss) aversion, which, however, tended to depend on baseline differences in WMC. These findings are consistent with animal studies reporting a causal link between D_1R activation and risky decisions (18,19). They also mirror findings in humans for whom blocking D_2R reduced risk aversion (13). The finding that increased D_1R stimulation reduces risk aversion in high WMC individuals informs a recent theoretical model of risky decision making (44), which links D_1-dominated states of striatal dopamine to reduced risk aversion. In contrast to the model predictions, we observed a lower preference for risky lotteries in the group with the highest D_1 agonist dose. However, when assuming an inverted U-shaped relationship between D_1R activation and decision making, one might reconcile our data with the theoretical model by arguing that only low levels of striatal D_1R activation reduce risk aversion, whereas high levels (as in the highest dose group) increase it.

At variance with our hypothesis, no significant effects of D_1R stimulation on time preferences were observed. This may appear surprising, given that preference for delayed rewards is canonically related to prefrontal cortex activity (45,46), which in theory should be influenced by the D_1 agonist. We cannot rule out the possibility that lower or higher doses of the D_1 agonist than the ones we administered might have shown an impact on time preferences. Still, it is interesting to note that also in the animal literature there is no clear link between D_1R activation and time preferences: enhancing D_1 activation was found to

reduce impulsivity (17), increase impulsivity (21,22), or have no impact on time preferences at all (47). It is conceivable that potential drug effects on striatal activation [which may be more strongly associated with preferences for immediate rather than delayed outcomes (45)] might have counteracted the drug effects on prefrontal activation. Following from this notion, future research on time preferences may want to disentangle the contributions of D_1Rs in the mesocortical system from those in the nigrostriatal system.

Together, the current data provide important insights into the causal function of D_1R activation for value-based decision making. D_1Rs are mainly expressed in 2 pathways: the mesocortical pathway [where D_1-dominated states lead to stable goal representations (5,6)] and the nigrostriatal pathway. Activation in both pathways might change a decision maker's sensitivity to goals or rewards at stake. For example, by enhancing prefrontal goal representations, D_1R activation might strengthen the focus on benefits (assuming the goal of maximizing benefits), which in turn motivates humans to tolerate larger costs. Alternatively, a recent computational model of striatal dopamine predicts that high dopamine levels increase the preference for options with the highest gain independently of the associated action costs (48). Theories about both prefrontal and striatal dopamine are thus consistent with our findings that the administered D_1 agonist modulated the sensitivity to risk and physical effort. While in humans the causal contribution of D_1R activation was mainly demonstrated for working memory functioning (49), the current work shows that D_1Rs are causally involved in economic choice as well.

Our findings speak to the clinical literature. Patients with schizophrenia (50) or Parkinson's disease (51) show increased effort discounting. It would be interesting to see whether these deficits can be counteracted with D_1R activation. Deficits in trading off risks against benefits were described for bipolar disorder (52) and schizophrenia (53). However, our findings also suggest that dopaminergic treatments of psychiatric disorders should consider baseline dopamine levels to avoid side effects of overdosing on decision making. In Parkinson's disease, treatment with D_3 and D_2 agonists is associated with impulse control disorders including increased risk taking and excessive gambling (54,55). Such undesired side effects could be minimized by adjusting therapy according to the relationship between risk taking and baseline levels as suggested by the current data.

Dopaminergic activity and economic preferences were hypothesized to follow a nonlinear (e.g., inverted U-shaped) relationship (23). This assumption might allow reconciling our finding of increased risk aversion under strong D_1R activation with theoretical claims linking D_1-dominated states to lower risk aversion (44). Also, the (trend-level) baseline-dependency of drug effects on prospect theory parameters is consistent with such an inverted U-shaped function between dopamine and risk preferences. It is also worth noting that increasing D_1R stimulation reduced cost tolerance in risky decision making but increased it in effort-based choice. This supports the assumption that the relationship between D_1R activation and various aspects of cognition follows a variety of functions with different optimal dopamine levels (23). However, with the range of doses used here, no strong conclusions can be drawn regarding the precise shape of the functions between D_1R activation and economic preferences.

Some limitations of the study need to be mentioned. First, it should be noted that the present pharmacological manipulation is systemic. The D_1 agonist acts both in prefrontal cortex, where it might impact decision-relevant cognitive processes, and in other regions containing D_1Rs such as the striatum, where the D_1 agonist might affect motivational rather than cognitive processes. Thus, while the result pattern is consistent with theories about prefrontal dopamine, changes in dopaminergic activity in other brain regions, particularly the nigrostriatal direct pathway, might have contributed to the observed effects as well. In fact, the lack of significant results in the time preference task might be explained by the opposing roles of prefrontal cortex and striatum in intertemporal decisions. Related to the lack of anatomical specificity, the current results are also agnostic with regard to which cognitive (e.g., working memory functioning) processes might mediate the observed drug effects on decision making. It should be noted, though, that under placebo, we observed no impact of WMC group on risk or effort preferences, which is at variance with the assumption that drug effects on working memory functioning mediate the effects on risk or effort preferences. Second, baseline synthesis capacity was measured only indirectly via working memory functioning. A direct measurement of baseline dopamine levels would have required the use of positron emission tomography imaging. However, previous studies provided evidence both for the reliability of WMC as proxy for dopamine synthesis capacity (29) and for dependency of pharmacological dopamine manipulations on individual baseline WMC (36,37). Third, this was a single-dose study, and the effects may have been more pronounced if repeated doses had been used.

To conclude, our data provide first evidence in humans that D_1R activation causally shapes economic preferences. Stimulating D_1Rs with a selective D_1 agonist modulated risk and effort discounting while leaving time preferences unchanged. Our results converge with theoretical accounts assuming that D_1-dominated states strengthen goal-related activation in prefrontal cortex and with a role of dopamine for economic choice.

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AS, RK, SD, DLG, NdM, BH, EF, AJ, and PNT designed research. AS, GG, and AJ performed research. AS analyzed data. AS and PNT wrote the manuscript. All authors approved final version of the manuscript.

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RK, NdM, and BH are former full-time employees of Pfizer and are currently full-time employees of Takeda. SD is a full-time employee of Pfizer and owns Pfizer stock. DLG is a former full-time employee of Pfizer and a current full-time employee of Cerevel. All other authors report no biomedical financial interests or potential conflicts of interest.

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